Intravitreal injections: A review of pharmacological agents and techniques

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Over the past three decades, intravitreal delivery of pharmacotherapeutic agents has advanced tremendously with many drugs being developed solely for intravitreal use. Intravitreal injections have now become routine in the management of various ocular conditions, most commonly diabetic macular edema and age-related macular degeneration, with the benefits of targeted therapy far outweighing the risks of the procedure. Herein we review the variety of agents available and currently being used for intravitreal therapy of various retinal and intraocular conditions, their indications as well as the optimal technique that should be employed in their administration.

Key words: Age-related macular degeneration, antivascular endothelial growth factor, bevacizumab, diabetic macular edema, endophthalmitis, intravitreal injections, ranibizumab

Intravitreal injections were first described at the turn of the 20th century when Deutschmann and Ohm used rabbit vitreous and air to repair retinal detachments in humans.[1,2] The use of intravitreal injection to administer medications was pioneered in the mid-1900s, with initial reports of intravitreal injections of antibiotics used to treat endophthalmitis.[3,4] However, the absence of adequate antimicrobial agents precluded the use of intravitreal injections beyond those of air and silicone oil, until the 1970s. The development of newer and safer antibiotics in the late 1960s and early 1970s fueled a renewed interest in their use as intravitreal injections to treat endophthalmitis. This was aided by poor results with alternate treatment of endophthalmitis. Two case series demonstrating the successful use of intravitreal injection of antibiotics to treat endophthalmitis were published.[5,6] The use of intravitreal injections to treat conditions other than endophthalmitis and retinal detachment did not gain momentum due to the perceived risk of the procedure. Even though ocular inflammation in animal models had been treated by intravitreal steroids in the 1980s, their use in humans was not reported until the late 20th century.[7] This was followed by reports of the use of 5-fluorouracil in the prevention of postvitrectomy fibroblast proliferation in patients with proliferative retinopathy,[8] and the subsequent use of intravitreal ganciclovir in the management of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).[9] The number of intravitreal injections performed has increased dramatically over the past decades, with intravitreal injections becoming one of the most commonly performed ophthalmic procedures as anti-inflammatory, antiviral, antibiotic, and vascular endothelial growth factor inhibitor (anti-VEGF) therapies have emerged as the standard of care in ophthalmic practice.[10]

The purpose of this review is to highlight the variety of intravitreal pharmacotherapy used in the treatment of human ocular diseases. We also demonstrate the techniques employed for the safe and effective administration of intravitreal injections.

Pharmacokinetics of Intravitreal Pharmacologic Agents

Intravitreal injections provide a logical method for physicians to overcome the blood-retinal barrier and ensure that therapeutic levels of the pharmacologic agent are achieved at the target tissue, thus circumventing systemic absorption and resultant toxicity of the agent. While several investigators have studied the pharmacokinetic properties of intravitreally administered compounds in animal and human models,[10-17] this still remains complex and incompletely understood. The vitreous is a hydrated, avascular, and gelatinous body containing 98%
water. Structurally it is composed of type II collagen and hyaluronic acid (forming <1% of total volume). The vitreous characteristics change with age, being more liquid and mobile with advancing age. There exist barriers between the anterior and posterior segments of the eye. However, injected substances tend to move throughout the vitreous body either by bulk flow in formed vitreous or by diffusion in liquid vitreous. Gradients exist between the vitreous and plasma formed by mechanisms including bulk flow and diffusion within the vitreous as well as the presence of physiologic blood-ocular barriers with reference to active and passive transport as well as intraocular metabolism. Factors that affect the clearance of pharmacotherapeutic agents from the vitreous cavity include alterations in normal anatomy and physiology of the eye as well as size of the compound injected. Mobile vitreous, vitrectomized eye, and aphakia or pseudophakia show an enhanced clearance of medications from the posterior segment.

The blood-retinal barrier in normal eyes prevents the development of adequate concentration of a systemically administered medication in the vitreous. The reverse holds true as well. Animal models of endophthalmitis have shown decreased half-life of intravitreal vancomycin (14 h) compared to noninfamed eyes (approximately 62 h). However, plasma concentrations of vancomycin were found to be higher in the former group compared to the latter, demonstrating a breakdown in the blood-retinal barrier. Another factor affecting the half-life of a drug in the vitreous is the size of the administered compound. Smaller size antibody fragments were found to penetrate up to the retinal pigment epithelium compared to full-length monoclonal antibodies, with consequently longer half-life in the vitreous of the latter compared to the former.

Pharmacologic Agents used for Intravitreal Administration

The pace of development of new applications for intravitreal injections continues to advance rapidly. In the past few years, several investigational products have received Food and Drug Administration approval for use in human ocular conditions. These include anti-VEGFs such as ranibizumab, pegaptanib sodium, and aflibercept (VEGF receptor blocker), intravitreal steroids, and steroid implants such as dexamethasone implant (Ozurdex, Allergan, Inc., Irvine CA, USA) and fluocinolone (Iluvien; Alimera Sciences, Alpharetta GA). Others are as yet studying the use of adenovirus vector-mediated gene transfer as well as stem cell injections to treat retinitis pigmentosa and age-related macular degeneration (AMD). Besides these, other classes of medications used via intravitreal administration for the treatment of various ocular conditions include antimicrobials in the management of endophthalmitis, gas, or air in the management of retinal detachments, tissue plasminogen activator (TPA) for submacular hemorrhage, and antiviral medications for the management of viral retinitis. While the content of this review is not exhaustive, it will acquaint the reader with commonly used intravitreal agents, their indications as well as injection techniques employed.

Antimicrobials

Experimental models of endophthalmitis in rabbit eyes were treated with intraocular antibiotics such as penicillin and sulfonamides as early as the 1940s. Favorable results were observed with penicillin in these cases. In the 1970s, recommended doses of intravitreal antibiotics were published after reports of favorable outcomes in acute postoperative endophthalmitis. Vancomycin was used in staphylococcal endophthalmitis and aminoglycosides in Gram-negative endophthalmitis. Ceftazidime, a third-generation aminoglycoside, has replaced aminoglycosides to overcome potential macular toxicity by the latter agent. To prevent retinal toxicity arising out of increased drug concentrations, the recommended doses [Table 1] of intravitreal antibiotics are very small and carefully titrated. It is advisable to prepare these injections under strict aseptic precautions, preferably under laminar airflow and by certified personnel.

<table>
<thead>
<tr>
<th>Intravitreal antimicrobial agents</th>
<th>Dose</th>
<th>Preparation</th>
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<tbody>
<tr>
<td>Vancomycin hydrochloride</td>
<td>1 mg/0.1 ml</td>
<td>Available in powder (500 mg). Add 10 ml of water for injection to get 50 mg/ml. Draw 0.2 ml of constituent into tuberculin syringe and dilute to 1.0 ml. This gives 10 mg/ml and hence 1 mg/0.1 ml</td>
</tr>
<tr>
<td>Ceftazidime hydrochloride</td>
<td>2.25 mg/0.1 ml</td>
<td>Available as 500 mg powder. Reconstitute with 2 ml water for injection to a concentration of 250 mg (active ingredient 225 mg) per ml. Withdraw 0.1 ml into tuberculin syringe and dilute to 1 ml by adding 0.9 ml diltuent. This gives concentration 22.5 mg/ml or 2.25 mg/0.1 ml</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2.25 mg/0.1 ml</td>
<td>Same as for ceftazidime hydrochloride</td>
</tr>
<tr>
<td>Amikacin sulfate</td>
<td>400 mcg/0.1 ml</td>
<td>Available as 100 mg in 2 ml vial. Withdraw 0.08 ml (4 mg) into tuberculin syringe and dilute to 1 ml to give concentration 4 mg/1 ml or 400 mcg/0.1 ml</td>
</tr>
<tr>
<td>Gentamicin sulfate</td>
<td>200 mcg/0.1 ml</td>
<td>Available as solution 80 mg/2 ml. Withdraw 0.1 ml (4 mg) into tuberculin syringe and dilute further with 1.9 ml of sterile water to give concentration of 4 mg/2 ml or 2 mg/ml (=200 mcg/0.1 ml)</td>
</tr>
<tr>
<td>Amphotericin-B</td>
<td>5 mcg/0.1 ml</td>
<td>Reconstitute 50 mcg vial with 10 ml of 5% dextrose. Withdraw 0.1 ml (0.5 mg) of solution and increase dilution to 10 ml with 9.9 ml of 5% dextrose to achieve concentration of 500 mcg/10 ml or 5 mcg/0.1 ml</td>
</tr>
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mg: Milligrams; ml: Milliliters, mcg: Micrograms
Over time, the emergence of antibiotic-resistant bacterial strains, especially the ocular and nasopharyngeal flora and pathogenic organisms responsible for ulcerative keratitis and other ocular infections, has become a major cause of concern. The resultant endophthalmitis has a more severe clinical presentation, worse visual outcomes, and challenging to treat. In such cases, treatment is usually commenced with broad-spectrum antimicrobials, with further therapy based on the culture and sensitivity reports. However, the concentration of intraocular drugs is usually above the minimum inhibitory concentrations of most pathogens and hence results in overcoming the in vitro resistance. Combination therapy is beneficial in polymicrobial endophthalmitis. To prevent complications such as precipitation and drug interaction, these are usually administered through different syringes. Micro precipitates that may be formed after intravitreal injections do not affect the therapeutic efficacy of these medications.

In the authors’ experience, the preferred intravitreal antibiotics in Gram-positive bacterial endophthalmitis are vancomycin and ceftazidime, and for Gram-negative, ceftazidime, amikacin, and gentamicin. The latter two have greater retinal toxicity making ceftazidime preferable. In the present day, gentamicin is avoided due to its macular toxicity and because of availability of less toxic agents. Based on the initial presentation, in the absence of culture reports, a combination of 2 antibiotic agents is used. Vancomycin and ceftazidime combination is ideal as it covers Gram-positive and Gram-negative organisms.

Fungal endophthalmitis is difficult to treat due to the absence of a wide variety of agents safe for intravitreal use. Systemically administered antifungal agents show limited intravitreal penetration. Amphotericin B has been used intravitreally to treat fungal endophthalmitis due to its broad-spectrum coverage. Doses of 5-10 mg intravitreal amphotericin have been used. However, recently, voriconazole was found to have better efficacy with reduced ocular toxicity and is being now used for intravitreal injection at concentrations up to 25 mg/ml.

Antivirals

The advent of intravitreal antiviral medications occurred in the 1990s for the treatment of CMV retinitis in the setting of human immunodeficiency virus infections. They have also occasionally been used in cases of acute retinal necrosis resulting from varicella zoster retinitis. The agents used mainly in the treatment of CMV retinitis include ganciclovir, foscarnet, and cidofovir. In the treatment of CMV retinitis, ganciclovir is administered at up to 2000 mcg in 0.05-0.1 ml concentrations, weekly. Ganciclovir can also be administered in the form of an intravitreal implant. Foscarnet has a shorter intravitreal half-life and needs to be administered twice a week at a dose of 2.4 mg/0.1 ml. Maintenance doses of the same are administered once a week. Foscarnet has been found to be useful in CMV resistant to ganciclovir. Combinations of intravitreal ganciclovir and foscarnet have been used effectively in patients who are unresponsive or fail to tolerate conventional therapy. Fomivirsen (Vitravene, Isis Pharmaceuticals Inc., Carlsbad, CA, USA) has also been studied for intravitreal use in patients with CMV retinitis, especially in situations where conventional therapy such as systemic and intravitreal ganciclovir, foscarnet, or cidofovir have failed or are contraindicated. Induction doses of fomivirsen are administered intravitreally at a dose of 330 mcg once every 2 weeks for 2 doses followed by maintenance therapy at same dose every 4 weeks. The drawback however for patients with AIDS-receiving intravitreal injections or implants of antiviral agents is that there is no coverage against infection either systemically or in the contralateral eye.

Vascular Endothelial Growth Factor Inhibitors

Anti-VEGFs have become a gold standard in the management of many retinal disorders in which neovascularization is the primary pathology. The main focus of this therapy has been in wet or exudative AMD. Anti-VEGF intravitreal injections have dramatically altered the prognosis of wet AMD and improved chances of preserving useful vision in these patients. However, anti-VEGF agents have also found use in the treatment of diabetic macular edema (DME) and are used adjunctively in cases of proliferative diabetic retinopathy as well as neovascular glaucoma. The drugs approved for use are pegaptanib sodium (Macugen, Pfizer Inc., New York, NY, USA), ranibizumab (Lucentis, Genentech, San Francisco, CA, USA), and aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA). Bevacizumab, a human monoclonal antibody, has been used off-label in the management of ocular conditions, whereas it is not approved for intravitreal use, it has found favor among physicians for its cost-effectiveness and prolonged half-life, which allows for a longer interval between treatments. It is used at a dose of 1.25 mg/0.05 ml. The authors follow an induction protocol of 3 injections at monthly intervals. Maintenance protocols are based on optical coherence tomography and clinical evidence of recurrence with injections administered as needed. Various studies and clinical trials have demonstrated the safety and efficacy of anti-VEGF agents in the treatment of wet AMD, DME, and ME arising out of retinal venous occlusion (RVO). Studies have recommended a monthly dosing schedule in the treatment of wet AMD with ranibizumab. However, other dosing regimens that include treat and extend as well as pro re nata (PRN; treat and observe) are also finding favor among clinicians due to lower injection numbers and favorable improvements in visual acuity. The approved dose for ranibizumab is 0.5 mg/0.05 ml for wet AMD and ME secondary to RVO; and 0.3 mg/0.05 ml for treatment of DME. Aflibercept inhibits VEGF-A and placental growth factor and its longer half-life allows for prolonged intervals between injections (~8 weeks). In the authors’ experience, aflibercept shows promise in patients with ME that is unresponsive to ranibizumab and bevacizumab. It is administered at a dose of 2 mg/0.05 ml.
Steroids

The principal effect of steroids is thought to be the stabilization of the blood-retinal barrier, reduction of exudation, and down-regulation of inflammatory stimuli. Steroids by virtue of their anti-angiogenesis and anti-inflammatory properties reduce the migration and activation of inflammatory cells. Steroids cause up-regulation of plasminogen activator inhibitor-1 (extracellular matrix protein), resulting in angiostasis. They also inhibit production of VEGF and stabilize the endothelial and basement membranes, thus reducing vascular permeability and leakage.

Topical steroids are unable to penetrate the posterior segment to achieve adequate therapeutic drug levels. Experimental studies conducted by Machemer et al. showed promise of intravitreal steroids in suppressing inflammation, cell proliferation, and neovascularization. Since then, intravitreal steroids have been studied extensively for the treatment of various posterior segment conditions such as cystoid ME, DME, choroidal neovascularization, and ME secondary to RVO with favorable outcomes.

Commonly used intraocular steroid preparations are triamcinolone acetonide (TA), fluocinolone, and dexamethasone. The dose of triamcinolone has been a matter of debate. While some studies have showed no significant benefit of 4 mg TA compared to 1 mg or 2 mg, Lam et al. demonstrated that while a higher dose (4 mg) resulted in sustained effect on vision and macular thickness, there were more associated ocular complications notably raised intraocular pressure (IOP) and cataract. The Diabetic Retinopathy Clinical Research Network (DRCR.net) has investigated the use of triamcinolone in DME with and without focal grid laser. It was found that while 4 mg of TA resulted in better visual acuity at 4 months, this was not sustained at 12 months. In a DRCR.net study comparing the use of intravitreal ranibizumab and TA with either prompt or deferred laser, it was found that ranibizumab with prompt or deferred laser resulted in better visual acuity and a greater decrease in macular thickness than either prompt laser alone or intravitreal TA combined with laser. It was also found that IOP-lowering medications were needed in 28% of eyes in triamcinolone group compared to ≤5% in other groups. In addition, cataract surgery was required in 55% of eyes in triamcinolone group compared to <15% eyes in sham or ranibizumab group. Studies have also showed promising results in patients with refractory or persistent DME. The SCORE (standard care vs. corticosteroid for retinal vein occlusion) study evaluated the use of TA in ME secondary to RVO showed beneficial effect in patients with chronic ME receiving 4 mg intravitreal TA compared to laser photoacoagulation. Improvement in ME was also noted in patients with nonischemic central RVO. Intravitreal TA has been used favorably in patients with Irvine–Gass syndrome, alone or in combination with anti-VEGFs in wet AMD as well as in combination with pars plana vitrectomy in proliferative diabetic retinopathy and proliferative vitreoretinopathy, as well as in the management of posterior uveitis and immunological disorders.

Dexamethasone demonstrates greater potency in inhibition of cytokines albeit with a shorter half-life compared to triamcinolone. It is administered intravitreally in the form of a biodegradable implant (Ozurdex; Allergan, Irvine, CA, USA) and is approved for use in RVO, noninfectious uveitis, and in DME patients, who are pseudophakic. Ozurdex is designed to have a sustained distribution of 700 mcg of dexamethasone in the vitreous cavity, with studies showing the presence of dexamethasone for up to 6 months in the vitreous with a peak during the first 2 months. Dexamethasone in clinical studies has showed improved visual acuity in eyes with RVO and ME, with significant reduction in the central macular thickness. Similar results were noted in eyes with Irvine–Gass syndrome or noninfectious uveitis and ME. DME treated with the dexamethasone-delayed delivery device, dexamethasone has also been used in combination with photodynamic therapy (PDT) in the treatment of wet AMD or as triple therapy (combination of PDT, anti-VEGF, and dexamethasone). Dexamethasone may be used in combination with intravitreal antimicrobials in cases of bacterial endophthalmitis to minimize inflammation-mediated tissue damage. Fluocinolone, a synthetic steroid with potency equivalent to dexamethasone but with greatly reduced solubility in the aqueous, allows for steroid release over a much longer duration compared to dexamethasone. Fluocinolone acetonide intravitreal implant (Retisert, Bausch & Lomb, Rochester, NY, USA) has been approved for use in noninfectious posterior uveitis and for DME (Iluvien, Alimera Sciences, Alpharetta, GA, USA).

Ocriplasmin

Ocriplasmin is a recombinant protease with activity against fibronectin and laminin. These form components of the vitreoretinal interface. Ocriplasmin (Jetrea, Thrombogenics, Iselin, NJ, USA) has been approved for the treatment of vitreomacular adhesion. It is administered at a dose of 1.25 mg/0.05 ml for the treatment of symptomatic and focal vitreomacular adhesions (≤1500 μ). It showed promising results in phase 3 clinical trials. However, there have been reports of acute vision loss and decline in visual acuity following its use.

Gas (Pneumatic Retinopexy)

Pneumatic retinopexy is an outpatient procedure that is used as an alternative to invasive surgery in the management of select cases of rhegmatogenous retinal detachment. It is a 2-step procedure in which the first step involves the injection of an expanding gas bubble intravitreally followed by positioning of the patient allowing the gas bubble to tamponade the break. This facilitates subretinal fluid resorption. In the second step, chorioretinal adhesion is induced using either cryopexy or barrage laser, or both. This is indicated in patients with a single, small superior retinal break (superior 8 clock hours
of the globe), extending <1 clock hour. A patient would need to maintain appropriate head position allowing optimal tamponade for >14 h/day for 5-7 days after the procedure.\[96\] The gases used for this procedure are fluorinated gases – C3F8 or sulfur hexafluoride (SF6). The volume of gas injected is 0.3 ml for C3F8 or 0.5 ml of SF6, filtered through a millipore filter into a 1 ml syringe with a 30 gauge needle. Prior to intravitreal injection of gas, a paracentesis is done to evacuate 0.3-0.5 ml of aqueous to lower the IOP. The intravitreal injection is performed 4 mm behind the limbus in phakic patients and 3 mm behind limbus is pseudophakic patients.\[94\]

The fluorinated gases used in this procedure are expansible gases. They draw the dissolved vitreous nitrogen, oxygen, and carbon dioxide into the infused bubble at a greater rate than the passive outward diffusion of fluorinated gas, leading to expansion of initial gas volume.\[97\] C3F8 gas expands to 4 times its initial volume over 96 h, whereas SF6 expands to 2.5 times initial volume over 48 h. The former maintains an effective presence in the vitreous for 4-5 weeks whereas for the latter it is about 1 week.\[97\]

Complications of Intravitreal Injections

Intravitreal injections if performed according to standard guidelines and protocols are a safe therapeutic intervention. However, they are an intraocular procedure and certain risks and complications have to be borne in mind. These include complications related to the procedure or to the intravitreal agent used. While an exhaustive overview of complications is outside the scope of this text, we have described the most common complications.

Complications associated with the procedure include peri-injection pain, hemorrhage (intraocular as well as subconjunctival), elevated IOP, wound leak, and ocular surface toxicity due to the use of pre-injection cleansing agents (such as povidone-iodine). Infectious endophthalmitis remains the most devastating complication after intravitreal injection. The incidence ranges from 0.019% to 1.6%.\[98\] With the advent of stricter injection protocols and advanced asepsis levels, there has been a decline in the incidence of endophthalmitis in recent studies compared to earlier clinical trials. The use of 5% povidone-iodine in the conjunctival fornices is universally accepted and strongly recommended to prevent endophthalmitis. The bactericidal properties of povidone-iodine are not diminished by the use of gel-based topical anesthesia, provided appropriate contact time is allowed.\[2\] The use of a sterile lid speculum prevents the contact of needle with lids and lashes.\[92,98,99\] The use of gloves is strongly recommended. Recent studies have emphasized the use of facemask and avoidance of talking on reduction of bacterial contamination.\[2,98,100,101\] The use of antibiotics before and after injection has not found to affect the incidence of endophthalmitis in these patients.\[98\]

The risk of rheumatogenous retinal detachment after intravitreal injection is very low, ranging from 0% to 0.67%.\[102,103\] Induction of a posterior vitreous detachment or an incorrect injection technique may contribute to this complication. It is advisable to use smaller gauge needle and marking out the site of injection (4 mm behind limbus in phakic and 3 mm behind in pseudophakic).\[98\]

There is an acute increase in IOP after intravitreal injection. This is related to the procedure and lasts for a few hours.\[98\] It is essential to perform indirect ophthalmoscopy after the procedure to examine the central retinal artery (CRA) perfusion. Paracentesis needs to be performed if IOP elevation causes CRA occlusion. Occasionally, the IOP elevation may be attributed to the pharmacological agent injected. This is either due to VEGF-blockade, inflammatory mechanism, or trabeculitis causing impaired outflow and damage to outflow pathways due to repeated injections may sometimes result in sustained IOP elevation.\[104\] This can be usually managed with topical antiglaucoma medications, and very rarely surgical management is needed.\[98\]

Certain antimicrobials used intraocularly may have retinal toxic effects. However, careful attention to the dose and concentration may help circumvent these effects. Macular infarction is a known complication of intravitreal gentamycin, especially if increased concentration of drug is injected.\[105\] Steroids are known to cause an increase in the incidence of cataract.\[73,75\] While anti-VEGF agents are usually not systemically absorbed after intravitreal injection, there have been reports of increased incidence of cardiovascular adverse events in these patients.\[16\] The authors prefer the use of ranibizumab to bevacizumab in patients with history of vascular episodes.

Injection Technique

In 2004, Aiello et al. published consensus guidelines for the practice of intravitreal injections.\[106\] Since then, the scope of intravitreal injections has seen a dramatic increase, both in agents used and indications for treatment. The current best practice patterns and guidelines for intravitreal injections are based on the recommendations of Aiello et al.

Prior to performing the intravitreal injection, it is important to take a written informed consent. The patient and their relatives must be explained about the risks and benefits of the procedure, as well as what to expect post-injection. The off-label use of medications must be explained and alternative options must be listed. For medico legal and safety purposes, it is essential to record pre-injection visual acuity and IOP. The pupil must be dilated. Examination of anterior segment of the eye must be performed to rule out blepharitis, conjunctivitis, or other infections.

The choice of location for performing the intravitreal injection is either in the office or in the operating room. Abell et al.,\[107\] in a retrospective review of more than 12,000 injections performed over 6 years, demonstrated a 0.12% (4/3376) per injection rate of endophthalmitis (3/3376...
culture positive; 0.09%) in office procedures, which was significantly higher than that reported when the procedures were conducted in an operating room setting (0/8873; \( P = 0.006 \)). Meyer et al.\(^1\) conducted a retrospective evaluation of 1844 injections and determined no difference in the rates of endophthalmitis in procedures conducted in the office without topical antibiotics (0.2%; 2/984 injections) versus inpatient procedures with topical antibiotics (0.23%; 2/860 injections). In a different retrospective, consecutive case series of over 11,000 injection procedures for various etiologies, an endophthalmitis rate per injection of 0.035\% (3/8647; 1 culture positive) in the office setting and 0.065\% (2/3063; no culture positive) in the operating room setting was reported.\(^{106} \) Based on these findings, it is essential to perform the intravitreal injection in a sterile environment with proper aseptic precautions. This may be an operating room or a sterile office setting as well.

Intravitreal injections are commonly performed using topical anesthesia. Various studies have evaluated the use of topical 4% lidocaine versus subconjunctival 4% lidocaine. While lower pain was reported during intravitreal injection with subconjunctival injection, the combined pain score of subconjunctival injection and intravitreal injections was not significantly greater than that of the topical group.\(^2,110\) Others have compared the use of topical lidocaine gel or pledget soaked in lidocaine to subconjunctival lidocaine and found no significant differences in the pain score.\(^{111,112} \) Based on these findings, the authors employ the use of topical proparacaine anesthesia followed by the application of a cotton-tip applicator soaked in proparacaine at the site of injection for 30 s.

The eye preparation povidone-iodine forms the crux of conjunctival surface preparation prior to injection. Typically 5% povidone-iodine solution is used. Of concern here is the contact time of povidone-iodine with conjunctiva and the use of anesthetic gels with povidone-iodine. It is recommended that povidone-iodine placed directly on the conjunctiva for at least 30 s to allow for maximum disinfection.\(^2 \) In addition, studies have showed that application of povidone-iodine after lidocaine gel decreases the efficiency of povidone-iodine.\(^2 \)

The use of peri-injection antibiotic medications is controversial. While most physicians, including the authors, preferring to prescribe antibiotics, recent studies report a significant increase in antibiotic resistance of ocular flora and a greater rate of endophthalmitis with use of topical antibiotics.\(^{2,113-115} \) Besides, no incremental benefit of peri-injection antibiotics was noted if adequate povidone–iodine prep was employed.\(^{116} \)

The injection is administered using a 30 gauge needle after placement of a sterile lid speculum. In order to prevent fluid reflux and vitreous incarceration in the wound, a sterile cotton-tip applicator may be applied to the site of injection while withdrawing the needle. The authors employ the conjunctival displacement technique prior to injection. This ensures that the conjunctival opening and scleral track do not overlap, allowing for sealing of the wound. After the injection, visual acuity may be evaluated and indirect ophthalmoscopy must be performed. The latter helps to assess CRA perfusion. Raised IOP can cause CRA occlusion. In this case, a paracentesis may become necessary.

Post-injection, the patient should be instructed to refrain from washing the eye with water for 24 h. The authors as mentioned employ the use of topical antibiotic eye drops for a week post-injection. The patient must be advised about warning signs such as pain, redness, discharge, decrease or loss of vision and to seek immediate medical attention if any of these develop.

**Conclusion**

Intravitreal injections have become a widely accepted method of treatment of various intraocular conditions such as neovascular AMD, DME, retinal vascular occlusions, proliferative diabetic retinopathy, and infectious and noninfectious uveitis among others. The safety and efficacy of this procedure has also been studied extensively. As newer agents are being introduced for intravitreal therapy, the treatment of once potentially blinding retinal disorders is now showing tremendous promise. However, as with any interventional treatment, protocols and guidelines need to be adhered to in order to have good outcomes.

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**Conflicts of interest**

The authors have no conflicts of interest to disclose.

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