

intravitreal drug delivery has become the gold standard for treatment of many retinal diseases, including neovascular age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion. The frequency of intravitreal injections has significantly increased since the introduction of vascular endothelial growth factor (VEGF) medications. The technique involved in properly performing this procedure is important to optimize patient safety and reduce the risk of complications.

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## Common Diseases Treated by Intravitreal Injections

1. Neovascular AMD
2. DME/NPDR/PDR (diabetic macular edema/non-proliferative diabetic retinopathy/proliferative diabetic retinopathy)
3. RVO (retinal vein occlusions)
4. Endophthalmitis
5. Uveitis
6. CME (cystoid macular edema)
7. CNVM (choroidal neovascular membrane) secondary to multiple retinal diseases

## Informed Consent and Risks of Intravitreal Injections

Discuss the indications, risks, benefits, and alternatives with patients. Obtain informed consent and have the patient's signature witnessed.

The **RISKS** of intravitreal injections include:

- Pain / foreign body sensation / epiphora (possibly due to dry eye, corneal abrasion, infection)
- Bleeding (subconjunctival, vitreous hemorrhage)
- Retinal tear / detachment
- Cataract (from inadvertently hitting the lens)
- Infection (endophthalmitis)
- Uveitis / retinal vasculitis (higher risk with brolocizumab)
- Loss of vision (from any of above)
- Loss of the eye (from a severe infection)
- Increased intraocular pressure with damage to optic nerve (primarily with steroids but may also occur after higher number of injections)
- Need for surgery (to address some of the complications above)
- Stroke/heart attack (with anti-VEGF medications, controversial)
- Off-label use (for bevacizumab, triamcinolone, other medications)
- Need for additional injections in future (patients need to understand this)

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- Voriconazole 50-100 micrograms/0.1mL
- Dexamethasone 0.4mg/0.1mL

## Anesthesia

Topical, subconjunctival, or pledgets are commonly used routes of local anesthesia for in-office intravitreal injections. The choice is based on physician preference, and is also dictated by how the patient tolerated prior injections. Retrobulbar block may need to be used in the case of endophthalmitis requiring a tap and injection. However, subconjunctival anesthetic is usually adequate and less painful than an already inflamed eye. An acute inflamed eye is generally a contraindication for intravitreal anti-VEGF injections, especially

Several studies have looked at the different anesthetic choices for intravitreal injections. One randomized controlled trial found that topical anesthesia was effective for most patients.<sup>[1]</sup> In this study, patients felt the least pain with the actual injection when a subconjunctival anesthetic was used. However, patients felt more pain when the actual anesthetic was being administered subconjunctivally. Therefore the collective pain score (injection pain + anesthetic pain) was greater for the subconjunctival group compared to the topical group (in which patients had less pain during the anesthetic, but slightly higher pain score during the actual intravitreal injection).

Topical tetracaine or proparacaine eyedrops can be effective. In a similar fashion, pledgets soaked with proparacaine or tetracaine can be used and allowed to rest on the globe over the area of planned injection for a short period of time. Another option is to use a gel type of anesthetic such as 2% or 4% jelly or Tetravisc. Some recent reports indicate that the gel may result in trapping of microbes on the ocular surface. It is recommended to apply betadine before and after the gel is placed. For subconjunctival anesthesia, typically lidocaine 1% or 2% without epinephrine is used.

Other points to remember:

- Subconjunctival anesthesia has a higher risk of causing subconjunctival hemorrhage
- Allow adequate time for anesthetic to take effect (can be as fast as 1 - 2 minutes for subconj, but would wait longer for topical)
- If a patient is very nervous or "jumpy" consider a subconjunctival injection so that the injection itself is not felt or minimized. Consider topical anesthetic prior to performing the subconjunctival injection to minimize discomfort.
- If using topical anesthesia (since patients feel the injection more), remind them immediately before the injection that the sensation will not move with the unanticipated sensation.

## Preparation for Intravitreal Injection

- Patient should be at least slightly supine with neck well supported
- Ensure that the headrest is secure and will not unlock during the injection (as patients have a tendency to get nervous, especially if they are back on the headrest)
- Close the door and make sure there are no distractions during the injection which could cause the patient to have an oculocardiac reflex
- Ensure that you have all required instruments before starting, as it is very uncomfortable for patient to wait once Betadine is applied
- Do a surgical "timeout" before the procedure to confirm the correct patient, correct eye, and any allergies. Preferably the technician or a nurse to help confirm with the patient prior to the procedure.

## Injection Site

- Superotemporally or inferotemporal for ease of access, though any quadrant can be used.
- Some retina specialists prefer the superotemporal quadrant, since should a complication such as a retinal detachment occur, it is easier to perform a pneumatic retinopexy. Others prefer the inferior quadrant as patients tend to look up with any squeezing of the lids (Bell's phenomenon).

## Asepsis

- Most important is povidone-iodine 5% solution as it has evidence based data showing risk reduction for endophthalmitis
- Antibiotic use is controversial, and most retina specialists do not pre-treat with antibiotics.<sup>[2]</sup> Historically, post-procedure antibiotics were used for approximately 3 days (likely for medico-legal reasons). Several studies have demonstrated that post-injection antibiotics do not reduce the risk of endophthalmitis.<sup>[3][4][5][6]</sup> More importantly, studies show increased antibiotic resistance with the use of post-procedure antibiotics.
- 5% povidone-iodine solution should be placed on the globe and allowed to sit on the eye for at least 30-60 seconds. One study showed that 10% povidone-iodine solution should be used to gently clean the eye and eyelashes. However, 10% Betadine is associated with more corneal toxicity so care should be taken.

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- indentation ring and nicely highlight the injection site.
11. Have the patient look away from the injection site. For example, if injecting the right eye in the superotemporal quadrant to the left.
  12. Hold syringe in dominant hand, and a cotton-tipped applicator in the non-dominant hand
  13. Do not talk and ask patient not to talk during the injection. Alternatively, wear a mask. Make sure the needle tip (which is absolutely sterile).
  14. Using your dominant hand, rest your wrist or pinky finger on the patient's face (forehead for superior and cheek for inferior stabilization)
  15. Insert the needle at the marked site in a smooth and single motion, aiming for the mid-vitreous cavity
  16. Insert the short 30g needle about 1/2 length in (to make sure you are in the vitreous cavity and not in the suprachoroidal space)
  17. Swing over with your non-dominant hand to push down on the plunger in a smooth fashion. (Note: some surgeons prefer two hands; the author feels that using two hands is more stable). Do not move the needle while inside the eye so as to not cause traction or cause a retinal tear/detachment.
  18. As you remove the needle, cover the injection site with a cotton-tipped applicator that is in your non-dominant hand
  19. Rinse the povidone-iodine out of the patient's eye
  20. Ensure optic nerve perfusion (patient should be at least light perception). Paracentesis is usually not required unless a large volume is injected. Some physicians prefer to check and document the IOP and do not let the patient leave until the IOP has reduced. Glaucoma patients may need an anterior chamber paracentesis as their outflow may be compromised. Injecting Kenalog can cause high IOP and it is not uncommon for patients to be temporarily NLP after the injection. Warn patients about this. Tip: apply anesthetic on the globe (e.g., anesthetic solution on a cotton-tipped applicator at the proposed injection site) to squeeze some aqueous humor out of the eye. Check IOP prior to injection and possibly prevent transient NLP vision.

## Post-Injection Care Tips

- Make sure to wash off povidone-iodine well so the patient does not have irritation/corneal toxicity
- Reassure patients that they may see floaters which are due to air bubbles or the medication itself (in the case of Kenalog or dexamethasone implant)
- Review endophthalmitis and retinal detachment symptoms and precautions
- Consider a follow-up phone call with patients 3-7 days after the injection
- A one week in-office follow-up is at the physician's discretion, but is not typically needed.

## Bilateral Intravitreal Anti-VEGF Injections

Intravitreal injections of anti-VEGF are traditionally given unilaterally. More recently, there has been an increase in the use of bilateral injections in patients with pathology in both eyes. Common diseases that may need bilateral injections include diabetic macular edema and neovascular glaucoma. There is evidence that the rate of bilateral involvement increases with the follow-up and disease duration.<sup>[13]</sup> A survey of retina specialists found that 46% of retina specialists perform bilateral same-day injections.<sup>[14]</sup> The purpose of bilateral same-day injections is to reduce patient burden in terms of office visits. In one study, more than 90% of patients strongly preferred bilateral injections to unilateral injections. However, some physicians will avoid bilateral injections for fear of bilateral endophthalmitis. Other local complications should be considered with bilateral injections, including inflammation/uveitis, raised intraocular pressure, retinal detachment and subretinal hemorrhage. Large gauge needle, and syringe are typically used for each eye to minimize risks.

There have been several large-scale studies of endophthalmitis in bilateral same-day intravitreal anti-VEGF injections. Overall, bilateral injections have a similar safety profile to unilateral injections. The largest study of 101,932 same-day bilateral intravitreal anti-VEGF injections in an academic private practice over 5 years found 28 cases of endophthalmitis (0.027% of total injections) with no cases of bilateral endophthalmitis. Similar studies have found the incidence of endophthalmitis from 0-0.01% to 0.065%.<sup>[17] [18] [19][20][21]</sup>

## Follow up

- Depends on the disease being treated and duration of treatment. Early on, patients may require monthly injections and follow-up. Once the disease is stabilized, some advocate extending the interval between injections permitting less frequent injections and follow-up.

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- prophylaxis to prevent endophthalmitis after intravitreal injection. *Ophthalmology*. 2014 Jan;121(1):283-289. doi: 10.1016/j.ophtha.2013.08.037. Epub 2013 Oct 18. PMID: 24144453.
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