Intravitreal Injection Guidelines

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With an increase in the number of intravitreal injections especially intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents the risk for endophthalmitis is a potential concern.

A meta-analysis by Jager et al. shows that the prevalence of endophthalmitis following intravitreal injections is low. They evaluated the incidence of endophthalmitis into infectious and non-infectious categories and found that the endophthalmitis rate was 0.9% (38/4382) per eye and 0.3% (38/14,866) per injection, when looking at both infectious and non-infectious cases. They also found endophthalmitis rate of 1.4% per injection for intravitreal triamcinolone acetonide and 0.2% per injection for intravitreal ranibizumab.

The risk of endophthalmitis after intravitreal injection may vary with various drugs. The reported incidence of endophthalmitis per patient in multicenter clinical trials with anti-vascular endothelial growth factor (VEGF) therapy ranged from 0.019 to 1.6%. Although cases of acute endophthalmitis following intravitreal bevacizumab (IVB) have occurred, the exact incidence rate remains unknown. The injection technique and compounding issues of bevacizumab remains the major areas of concern. Ranibizumab comes as a single use vial so the concerns are limited to injection techniques.

These guidelines are framed to reduce the risk of endophthalmitis by streamlining the compounding and injection techniques with special reference to bevacizumab.

The risk for endophthalmitis following Intravitreal Injections could be:

1. Drug related:
   a. Counterfeit medication
   b. Lapse in cold chain

2. Procedure related
   a. Multiple use of multi-dose vial
   b. Injection technique
   c. Aseptic precautions

Drug related

This concern is more with off label drugs like bevacizumab.

Counterfeit medication

There are reports of counterfeit medications across the world for bevacizumab. In 2010–11, the concern was raised in China and the USA.

How to address and make sure that the drug is not fake?

1. Check the authorization letter of the bevacizumab dealer and buy the drug from a certified Roche dealer. Since the use in the eye is off label, the dealers may not have the authorization for supply to the ophthalmologists. We can inspect the authorization and bills from Roche periodically.

2. Check the drug license of the dealer.

Cold chain lapse

Bevacizumab can be stored at 2–8°C for 45 days. Roche monitors the cold chain on its server till it transports to the authorized dealer. The company also monitors and maintains a log of cold chain at the storage facility of the dealer.

Our suggestions

- Inspect the cold chain maintenance of the dealer.
- Verify that the drug has not been kept in stock for a long period.
- Check how long does the dealer stocks the drug.

Storage

Once purchased, check that the drug is brought in a dry ice pack preferably with a temperature monitoring device.

It should be stored at the hospital refrigerator at 2–8°C in a dark place with temperature display, power backup, and a temperature log. Electronic data loggers are available in the market to monitor the temperature.

The drug should be kept under lock so that limited people have the access to it and refrigerator is not opened again and again to avoid a lapse in cold chain.

Injection procedure related

How to use the multi-dose vial of 4 ml?

The study by Bakri et al. shows that the drug can be kept in capped disposable 1 ml syringes when stored at 2–8°C with minimal loss of efficacy over 1 month, but there is no level 1 evidence for sterility. There are published articles for compounding the drug in aliquots for multiple use but there are reports of endophthalmitis resulting from compounding issues.

We suggest opening a vial and preparing the required number of injections under sterile conditions and storing in different sterile boxes to be used within few hours if it has to be used by...
different surgeons in different operation theatres on the same day within the same theatre complex. One box can be sent to each operation theatre with the required number of filled syringes. It is preferred to do the injection procedure in operation theater or a sterile room designated for such procedures.\textsuperscript{7,8}

\textbf{Preparation of multiple syringes for use on a given day}

- Note the batch number of the drug so that it can be helpful for tracking, in case of endophthalmitis.
- To check the bevacizumab vial for expiry date and label by the technician.
- Opening of the vial and cleaning of rubber lid by alcohol wipes.
- 18/20 G needle is inserted in the rubber lid of vial by a scrubbed paramedical staff in the operation theatre with mask and cap with minimal talking. Instead of using the 18/20G needle for puncture an instrument called mini-spike (Braun) can be used to prepare multiple syringes to avoid contamination.
- The vial must be held upside down by non-scrubbed personnel in the operation theater wearing a cap and mask.
- The scrubbed staff can withdraw 0.2 cc of bevacizumab in a 1 cc disposable syringe and cap it with the needle.
- Prepare the number of injections required for the day by withdrawing drug from a single puncture by 18/20G needle.
- The prepared capped syringes with the drug can be stored in separate boxes depending on the number of surgeons giving the injection on the given day. The boxes can be kept in a refrigerator maintained at 2–8°C and should be used on the same day.
- One syringe can be sent for bacterial culture sensitivity testing so that on follow-up of these patients the report can help us to decide the next plan of action in case of infection.
- Preparation of similar aliquots in a sterile environment under a laminar hood is also described.

\textbf{Injection technique}

- The literature suggests that prophylactic antibiotics are not better than the use of povidone iodine 5% drops for a contact period of 5 minutes in the conjunctival cul-de-sac.\textsuperscript{9–12}
- Patients with doubtful hygiene, one eyed and with known povidone allergy, can have either 3 days of topical fluoroquinolones or pulse dose of fluoroquinolone eye drops on the same day of injection.
- We suggest that the injector has a proper scrub wears disposable mask, and gloves. If in operation theatre, cap is mandatory.
- The eye lids and lashes should be scrubbed with 10% povidone iodine solution and eye should be draped.
- Lid speculum should be used to avoid the contact of eye lashes with the injection site. Use of lid speculum is reported to reduce the risk of endophthalmitis in the intravitreal injection procedure. Contact of the needle with eyelashes should be avoided.\textsuperscript{13–15}
- Injection can be administered after the use of sterile proparacaine eye drops.
- The needle used to cap the drug syringe for storage should be replaced by a 30G needle for injection.\textsuperscript{16}
- Oblique scleral entry is preferred over perpendicular injection to prevent reflux of vitreous and wick related endophthalmitis.\textsuperscript{16–19}
- Any quadrant can be chosen for injection (infero-temporal quadrant is preferred, particularly for opaque drugs which otherwise can cause significant visual disturbance, e.g. triamcinolone). Sterile calipers can be used to measure 3–4 mm from limbus (depending on lens status) to mark the injection site.
- Usage of mask is a must. Avoid talking while giving the injection. Gram-positive cocci are the commonest infections following intraocular injections and droplet infection may be the source.\textsuperscript{12,20,21}
- The eye can be patched with povidone iodine 5% drops for 2 hours after injection.
- Patients should be examined on post injection day 1 and 3. We suggest a good examination of anterior segment using slit lamp and fundus using indirect ophthalmoscopy. Also check intraocular pressure using Applanation tonometry. It is preferable to see the patient on the third post injection day as most of the endophthalmitis after bevacizumab have occurred between 2 and 5 days.
- Patients should be instructed to avoid head bath for 1 day post injection and swimming for 3 days post injection.
- Post injection antibiotic prophylaxis should be reserved for one-eyed patients and patients with doubtful hygiene or with iodine allergy. Most of the studies suggest no role of antibiotics in post injection period.
In case the patient is due for injection in both eyes, it should be done at an interval of 3 days to avoid an increased level of circulating drug in the system. Some studies suggest that separate batch number of the vials may be used for the two eyes in case bilateral injections are required on the same day.

- Anti-VEGF injections should be deferred in pregnant ladies or people with uncontrolled hypertension or increased risk of thromboembolic phenomenon or recent history of stroke or myocardial infarction.

- Injections should be avoided in people with uncontrolled blood sugar levels as it may in turn increase the chances of endophthalmitis.

**Discarding the unused drug**

It is preferable to discard the unused drug and destroy the label.

The bottle can be discarded as per the norms.

**References**


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