GUIDELINES FOR INTRAVITREAL INJECTIONS

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The incidence of post-injection endophthalmitis though low, is of great concern as there is a dramatic increase in the number of injections performed annually in India. The risk of cluster endophthalmitis is high as multiple patients may receive injections from the same vial in a single session.

Cluster Endophthalmitis occurs due to:

Contaminated surgical supplies, Sterilization failure or Improperly performed technique. Commonest cause of contaminated surgical supplies is a Counterfeit Bevacizumab vial.

Following draft has been developed jointly by AIOS and VRSI under the guidance of Prof Atul Kumar.

We understand that there may be techniques, other than the ones enunciated in this draft, and working well in hands of some retina surgeons in India. However the recommendations made in this draft are based on the Best Practices followed and published worldwide. Our aim is to allow each one of us in India to achieve safe intravitreal injection of Bevacizumab (Bevacizumab) for our patients with an endpoint of zero infection.

{Please remember, this is only a Best Practice Guidelines Document and has no legal binding}

Background of this Document:
Based on the recent meeting held on 8th February 2016 between Dr V G Somani Joint DCGI, a panel of experts from all over India, representatives of the All India Ophthalmological Society (AIOS), Vitreoretinal Society of India (VRSI) and representatives from the Roche
Products (India) Pvt. Ltd it was decided that Ophthalmologists in India can use Bevacizumab as an off label drug for Intravitreal injection. This should be done after taking an informed consent from the patient who should be informed about the options available. The injection should be performed in a sterile environment and should be done by Ophthalmologists, who have the knowledge and training of performing safe intravitreal injections and have the ability and the facilities to manage any adverse events that may arise after such an injection.

ROCHE COMPANY, who is the manufacturer and supplier of Bevacizumab in India, will be responsible for delivering pure and sterile Bevacizumab Vials with a documented cold chain to its distributor. Once procured from the distributor it is the duty of the Ophthalmologist to maintain the sterility and cold chain of the Bevacizumab vial and to deliver it safely in a sterile environment to his/her patients.

Following document discusses the recommended way Bevacizumab should move from the Distributor into doctor’s clinic/hospital and further used as an intravitreal injection. It will help you achieve the goal of safe delivery of sterile Bevacizumab.

A) Procuring and Storing Bevacizumab Vial
B) How to Use Bevacizumab Vial
C) Bevacizumab Intravitreal Injection Procedure
D) Post Injection Patient Monitoring and reporting of Adverse Events

A. PROCURING & STORING THE BEVACIZUMAB VIAL

1. Purchase drug from a ROCHE authorized distributor (List will become available on www.rocheindia.com or the dcgi website) only on a proper bill that documents the lot number and matches with the lot number on the carton.

   Please ensure he/she is an authorized Roche Distributor. It is best to avoid switching dealers for the sole purpose of discounted price. Check the authorization letter of the dealer. We can inspect the authorization and bills from Roche periodically. We are working to get the label modified so that the drug can be purchased on the prescription of an Ophthalmologist or an oncologist.

2. Check the Cold chain log record (from Roche to the Final Distributor). This may not be possible for each vial but should be asked for and checked periodically.
3. Bevacizumab carton may preferably be stored in an airtight (screwable) clean plastic container to prevent wetting of the carton at 2–8°C. Once purchased, transport the drug in a dry ice pack.

4. It should be stored at the hospital in an exclusive refrigerator at 2–8°C with temperature display, power backup, and a temperature log. Do not store any non-drug related items, such as food and beverages, microbiology or pathology samples, blood and blood products, in the same refrigerator. Electronic data loggers are available in the market to monitor the temperature. The refrigerator should ideally be lockable and access to this should be possible only to few certified people.

5. A separate register should be kept to keep record of Bevacizumab usage. This should have following information
   a) Name of the Person who transferred the vial to the refrigerator
   b) Record of Utilization of the vial with the lot number, aliquot preparation date and samples sent for culture and their reporting.
   c) In case the culture comes positive, report to the distributor and inform on the national registry with the lot number (this registry is being developed)

_Fractionation procedure guidelines (For a complete understanding, please refer to the video on the VRSI website www.vrsi.in/ Bevacizumab. This video will soon become available,_

**B. HOW TO USE THE BEVACIZUMAB VIAL**

There are options to ensure safe injections of Bevacizumab into the vitreous which are listed below. The person (paramedical staff/doctor) who removes the vial from the refrigerator should enter his /her name in the Bevacizumab register

_To ensure authenticity of the Bevacizumab vial please check that the carton has not been tempered with and then use the Kezzler code on the carton. This is an alphanumeric code that needs to be sent as an sms to the number indicated on the vial. You will get an instantaneous reply from ROCHE about the authenticity of the vial. Use the vial only after authenticating it. If the code is not correct do not open the carton and use the vial. Return it with the proof of the message you have got to the distributor._

Once the authenticity is confirmed, carefully open the vial and check that the lot number and expiration daye on the vial matches that on the carton. Also ensure the vial does not look tampered and look at the contents of the vial for anything unusual.
OPTIONS FOR PREPARING BEVACIZUMAB

Option 1:

Prepare aliquots in class 1000 environment under a class 10 laminar flow hood and thermosealed.

Option 2:

Fractionation and Aliquoting:

Place of Fractionation

We suggest opening a vial and preparing the required number of injections in 1ml syringes under sterile conditions (ideally under ISO class 5 conditions):

- Clean Room with Laminar flow Hood
- Compounding Isolator
- Sterile Operation Theatre with HEPA filter or Laminar flow with filter.

Steps of Aliquoting

- Open the cap of the vial. Clean the Rubber Stopper with Sterilium/ 70% Isopropyl Alcohol. The swab used for cleaning also must be sterile. A 20/23 G needle / mini spike device is inserted in the rubber stopper of the vial by a scrubbed paramedical staff / ophthalmologist in the operation theatre with mask and cap. The scrubbing and gowning should be as for any intra-ocular surgery. The vial must be held upside down by non-scrubbed personnel in the operation theater wearing a cap and mask.

- Do not talk while the procedure is being done.

- The scrubbed staff should withdraw 0.2 ml of Bevacizumab in a 1 ml disposable syringe without injecting any air in the vial. All other aliquots are similarly prepared.

- Cap it with a 30 G needle. Ensure there is no remnant air in the syringe. The needle could be optionally bent/ capped by a sterile cap.

- Do not withdraw less than 0.2 ml per syringe. All syringes should be prepared by withdrawing drug from a single puncture of 20/23 G needle.

- The prepared capped syringes with the drug must be stored in ETO sterilized sealed pouches and then placed in a sterile autoclavable container. Each sterile box should have a label with name of the drug, batch number, date of preparation of the syringe and date of expiry, (which is 2 weeks from the date of preparation). Each sealed cover of the syringe must have an individual label of the batch number and date of expiry of the syringe. The sterile autoclavable box is to be kept at 2-8°C. On the day of consumption the required number of syringes can be taken out in the OT, in sterile conditions.
environment and the rest transferred to another sterile autoclavable box and restored.

- Even if all the injections are to be consumed the same day by different surgeons in the same hospital, they should be maintained between 2-8°C.
- Two of the aliqotted syringes should be sent on day 1 for microbiological culture.
- All the boxes be kept at 2-8°C
- A freshly opened 29/30/31 G needle should be used at the time of performing the Intravitreal injection.

A separate register for maintaining a log of usage of Bevacizumab must be maintained in the operation theater. This includes medical record number, name of the patient, name of surgeon, and indication for use, and the batch number with expiry of the syringe.

Two syringe must be sent for culture and sensitivity testing. If there is no growth on culture after 48 hours, the batch of syringes can be released for use in patients.

It is preferable to keep the vial for a month before destroying it. The vial should be destroyed rather than just discarded to prevent its misuse. Destroy the labeling sticker on the vial with a permanent marker or remove it physically before discarding the vial.

**Option 3:**

Withdraw Bevacizumab directly from the vial using a 30G needle by strict aseptic technique (after having cleaned the rubber stopper with Sterilium or 70% Isopropyl alcohol) in a sterile OT and inject. **Ensure that before you start injecting the first aliquot, send a sample for culture and sensitivity, wait 48 hrs to obtain a negative culture.** The injection can be done only if the culture is clear. This technique has limited published data and hence has to be followed with caution and at the discretion of the ophthalmologist under very strict aseptic conditions. The vial should always remain stored after use in its carton and in an airtight plastic container at 2-8°C.

It is recommended that both for technique 2 and 3, a culture is to be sent on day 1, wait for 48 hours for culture report before using the aliquots or the vial. The 30G needle used for injection should be a new one and not the one with which the aliquot was stored. The vial or the aliquots can be stored, kept and used for a maximum duration of two weeks.

- **Discard the empty vial after one month— it is NOT to be re-used**
C. Intravitreal injection guidelines (Please see video at www.vrsi.in/ Intravitreal injection (This will be soon uploaded))

1. Pre-op preparation and precautions:
   • Patient screening & precautions:
     • The need and choice of Intravitreal injection should be tailored to the individual patient according to the best clinical judgment of the attending/injecting eye specialist.
     • All patients should be screened to ensure a patent nasolacrimal duct and negative regurgitation test.
     • Patients with active infection of the ocular adnexa (blepharitis, meibomitis) or a blocked nasolacrimal duct/positive regurgitation test are at high risk for endophthalmitis and should be treated for the active infection first. Injection should be scheduled after the active infection is treated.
     • Surgical/procedural time-out to verify the patient's name, Intravitreal agent and laterality should be practiced before injection for each patient.
     • Bilateral injections are NOT recommended and injection for the other eye should be planned at least one week later.
     • Patients with uncontrolled systemic conditions like uncontrolled diabetes should first be treated for it.
     • Antibiotics: Routine use of topical antibiotics for a day prior and three days post injection may be of help.
   • Patient preparation:
     • Consent: An informed written consent should be taken from all patients undergoing the injection after explaining the procedure and the risks involved. Off label use of Bevacizumab should be included in the consent and explained to the patient.
     • Each patient should be given a cleaned OT gown, protective cap and booties before entering the preoperative holding area/operating room.
Time of Using the Alliquoted Bevacizumab

- While the Aliquots are waiting to be used they should be maintained in sterile, packed pouches in a sterile container at 2-8°C. Local logistics need to be worked out by the injecting surgeons.

- The drug is not to be stored for more than 15 days.

2. Steps of Injection

1. It is recommended to do the injection procedure in an operation theater or a sterile room designated for such procedures taking all precautions as are taken for any intraocular surgery. We do not recommend Intravitreal injection Bevacizumab in an office setting.

2. Evidence suggests that prophylactic antibiotics are not better than the use of povidone iodine 5% drops. We recommend mandatory cleaning and draping. Use 10% povidone-iodine to clean the skin and periocular adnexa and 5% povidone iodine drops to be instilled in the conjunctival sac for a contact period of 3 minutes.

3. Please instill one drop of proparacaine eye drops in the eye before instilling povidone-iodine drop.

4. Patients with known povidone allergy can have fluroquinolone eye drop instilled 3 times in the eye starting 30 minutes prior to the injection.

5. The surgical area should be draped using sterile linen and a separate plastic sticking eye-drape for each patient to isolate the field.

   - A sterile speculum should be used to prevent contact of the eyelashes and eyelid margins with the injection site and needle.

   - Topical anesthetic drops should be preferred over anesthetic gel as the latter may interfere with povidone-iodine contact with the conjunctiva/injection site.

   - Reapply povidone-iodine after anesthetic drop use. Before the injection, povidone-iodine (5%) should have been the last agent applied to the intended injection site.

   - Routine anterior chamber paracentesis is NOT recommended.

6. The injecting physician must scrub, and wear cap and mask. Talking should be minimal during the injection procedure.

7. Draping should be done after a minimum of 2-3 minutes of povidone iodine painting. This is to provide adequate exposure time for the povidone iodine to act against pathogens.

8. During the waiting time of 2 minutes, one can prepare the caliper marking, and make the final adjustment of volume of Bevacizumab with a fresh 29/30 G needle.
9. Do not hesitate to re-drape if eyelashes have not been completely tucked under the drape.

10. Take a final time-out to confirm the name of the patient and the correct eye to be injected.

11. It is preferable to inject under an operating microscope.

12. Any quadrant can be chosen for injection. Sterile calipers should be used to mark 3–4 mm from limbus (depending on lens status) to mark the injection site.

13. Post injection the cul de sac can again be flushed with povidone iodine or the injection site dabbed with a povidone iodine soaked sterile swab.

14. The eye can be patched with povidone iodine 5% drops for 2 hours after injection.

15. Post-injection antibiotic and its use is left to the discretion of the Ophthalmologist treating the case. However, in patients with poor lid hygiene, or debilitating systemic status, topical antibiotic eye drops for 5 days are recommended.

3. Post-operative precautions:

   • Proper lid hygiene should be maintained in the post-op period
   
   • Post-injection IOP should be monitored and topical antiglaucoma may be prescribed for post-injection IOP spike as and when warranted.
   
   • All patients should be given a discharge card mentioning the injection details, postoperative instructions, symptoms of infection (pain, redness, dimness of vision, swelling, discharge, etc.) and 24-hour emergency contact information.
   
   • Patients should instructed to avoid washing of eyes for 24 hours
   
   • After each day, all the instruments and linen after thorough cleaning and drying should be autoclaved for the next day.
   
   • Follow-up of each patient should be tailored as per the indication for the Intravitreal injections.

D. Postoperative Management

1. Patients may be examined within 3 days after injection. If the patient is unable to come for any reason, the patient must be asked to report to the nearest ophthalmologist immediately if there is unusual pain, redness, or drop in vision at any time. These instructions must be given in writing to the patient and it must be ensured that they, or the accompanying attendant have understood it.

2. We suggest a good examination of anterior segment using slit lamp for any cells in the anterior chamber or anterior vitreous. Fundus should be examined using indirect
ophthalmoscopy for any exudates, floaters, or new onset peripheral retinal hemorrhages or vasculitis.

3. Please check the intra-ocular pressure at each visit.

4. Patients should be instructed to avoid head bath for 1 day post injection and swimming for 3 days post injection.

5. In case the patient is due for injection in both eyes, it should be done at an interval of 3 days

Cautions

- Injections for ROP are not covered in these guidelines.

- Anti-VEGF injections should be deferred in pregnant women.

- Caution should be exercised in patients with increased risk of thromboembolic phenomenon or recent history of stroke or myocardial infarction, as for any other intra-ocular surgery.

- Injections should be deferred in patients with uncontrolled blood sugar levels as it may increase the chances of endophthalmitis. However, there is no evidence-based guideline for a cut-off of blood sugar or HbA1c level.

- Patient should be informed about higher risk of endophthalmitis in uncontrolled diabetes. If the patient wishes to proceed with the injection due to unavoidable circumstances, the above discussion should be documented in the consent prior to the injection. Such patients may be given pre and post-injection topical antibiotics as an additional precaution.

Don’ts

Do not buy Bevacizumab from a Non Roche Distributor

Do not use the Bevacizumab Vial if not Authenticated by Kezzler Code

Do not inject Bevacizumab in Office. Considering the varied circumstances in India we have taken a conscious decision of injecting Bevacizumab in sterile setting of an operating room or similar area.

Do not transport partially used vials in ice packs. Do not transport Aliquoted syringes of Bevacizumab. If a surgeon is practicing at multiple centers, it is recommended that each center be equipped to fractionate Bevacizumab. If this is not feasible, it is recommended that the patient be taken to the nearest center where Bevacizumab is available.

Do not store an Bevacizumab vial for re-use once it’s seal is broken
Do not re-use the Bevacizumab vial by puncturing it multiple times.

These guidelines may be updated as and when new evidence is gathered by us or any other Indian / Western scientific body. Visit www.vrsi.in for any updates and to report adverse events.