Consensus on the Intravitreal Injection Technique among Infants with Retinopathy of Prematurity by the Vitreo-Retina Society of the Philippines

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Retinopathy of prematurity (ROP) is a potentially-blinding vaso-proliferative disease that may occur in infants born <32 weeks, those born with birth weight of ≤1500 g, or those born 32-36 weeks but with unstable clinical course (severe sepsis, blood transfusion within the first 10 days due to anemia, oxygen use especially if without oxygen blender, and high risk infants as assessed by the neonatologist).[1-7] Management of ROP varies depending on the stage of the disease ranging from observation,[8,9] laser treatment,[9] to surgery.[10]

Several studies have shown the role of vascular endothelial growth factors (VEGF) in the pathogenesis of ROP.[11,12] There is growing evidence that intravitreal injection of anti-VEGF provides favorable outcomes in the management of ROP.[11,12]

In the BEAT-ROP study (Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity), intravitreal bevacizumab showed significant benefit over conventional laser therapy for stage 3+ ROP within zone 1. The study also noted that there was continued vascularization of the peripheral retina after intravitreal bevacizumab, whereas conventional laser therapy destroyed the peripheral retina and caused permanent visual field defects.[13]

In the RAINBOW study (Ranibizumab Versus Laser Therapy for the Treatment of Very Low Birthweight Infants with Retinopathy of Prematurity), premature infants treated with ranibizumab 0.2 mg were twice as likely to achieve clinically significant treatment success compared to infants treated with conventional laser.[14] In September of 2019, 0.2 mg ranibizumab was approved by the European Commission for the management of ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or aggressive posterior ROP (AP-ROP) disease.[15]

Intravitreal injection of anti-VEGF is now an acceptable option for the treatment of ROP, however, publications about the intravitreal injection technique among infants are scarce. Considering the anatomic differences between adults and newborns, the Vitreo-Retina Society of the Philippines (VRSP) found the need to create guidelines in the Philippine setting for the performance of intravitreal injections among infants.

I. All intravitreal injections for ROP should be performed by a member of the VRSP or the Philippine Society of Pediatric Ophthalmology and Strabismus (PSPOS). A Philippine Board of Ophthalmology (PBO) certified member of the Philippine Academy of Ophthalmology (PAO), who is knowledgeable, skilled, and comfortable in the diagnosis and comprehensive management

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of ROP, may inject anti-VEGF agents in infants with ROP if performed under the guidance of a VRSP or PSPOS member. This is an option if no VRSP or PSPOS members are available in the locality.

II. Clinical Setting of Care
The procedure may be performed in either an operating room, a room designated for intravitreal injections, a neonatal intensive care unit, a nursery, at bedside, or in the clinic as long as the venue for the injection is adequately clean.[16]

III. Preprocedural Issues

A. Informed Consent[17]
   a. Informed consent forms specific for intravitreal injection and specific for the off-label use of anti-VEGF agents for ROP have to be signed prior to the procedure.
   b. The consent form should include the name of the drug to be injected, the indication for injection, and the potential risks and benefits of the use of anti-VEGF agents and of the procedure itself.
   c. Information must be fully explained to the parents of the infant.

B. Pediatric Clearance
   a. The benefits, risks, and indications of anti-VEGF injections should be carefully considered in premature babies, especially if with systemic comorbidities.
   b. The necessity for a pediatric clearance will be at the discretion of the attending ophthalmologist.

IV. Surgical Site Preparation

A. Intravitreal injections in infants are intra-ocular procedures that require adherence to principles of asepsis and sterile technique as for other conventional intraocular surgeries.

B. There is no robust evidence to support that the instillation of a topical antibiotic eye drops before the intravitreal injection reduces the risk of subsequent intraocular infection.[18,19]

C. The infant's pupil/s may be dilated using a combination of 0.5% tropicamide and 0.5% phenylephrine to start at least 30 minutes before the scheduled time of injection. Excess eye drop should be wiped off immediately from the skin and punctal occlusion with a finger may also be done for 3-4 minutes after instillation of the mydriatic drops to decrease systemic absorption and to minimize possible systemic adverse effects.[20]

D. Preoperative disinfection of the periocular skin with 10% povidone-iodine and a minimum exposure time of 3 minutes is suggested.[21] Aqueous chlorhexidine in minimum amount to avoid chemical skin burn may be used as an alternative in infants with hypersensitivity to povidone iodine. Wipe off any excess solution immediately to prevent skin irritation.[22]

E. The use of a newly opened bottle of topical anesthetic eye drops is advised.

F. Povidone iodine 5% should be applied onto the conjunctival cul-de-sac or lower fornix with a minimum contact time of 30 seconds.[23] Chlorhexidine 0.05% to 0.1% may be flushed on the lashes and lids in infants with hypersensitivity to povidone iodine.[24] Wipe off any excess solution immediately to prevent skin irritation.[22]

G. The use of a sterile solid-blade lid speculum is recommended to isolate the lashes from the site of injection.[16, 23, 25]

V. Injection Procedure

A. Intravitreal injection is performed under topical anesthesia.

B. A competent assist is important to gently position and secure the head of the swaddled infant during the injection.[26] If the infant is on mechanical ventilation, the arms must be secured and the head be held by the assistant during the injection.

C. As part of good surgical practice, the donning of sterile surgical gloves[16] and the wearing of a surgical mask[27] are advised.

D. The injection site varies depending on

the age of the infant with much care to avoid iatrogenic retinal tears and injury to the globular crystalline lens of the infant (Table 1).

Table 1. Intravitreal injection site in patients with retinopathy of prematurity

Intravitreal Injection Site for Retinopathy of Prematurity[28]	
Post-Menstrual Age, weeks	**Distance Posterior to Limbus,* millimeter**
34	1.6 - 2.1
35	1.6 - 2.1
36	1.6 - 2.1
37	1.5 - 2.0
38	1.5 - 2.0
39	1.4 - 1.9
40	1.4 - 1.9
41	1.4 - 1.9
42	1.3 - 1.8
43	1.3 - 1.8
44	1.3 - 1.8
45	1.2 - 1.7
46	1.2 - 1.7
47	1.2 - 1.7
48	1.1 - 1.6

* It was recommended that nasal sclerotomies be 0.25-0.5 mm shorter than the recommended location.

E. The present recommendation is to inject half of the adult dose (0.625 mg/0.025 mL for bevacizumab,[13] 0.2 mg/0.025 mL for ranibizumab[14]), preferably at the temporal quadrants in a vertical orientation parallel to the visual axis to avoid hitting the lens (Figure 1).[29] The optimum dose for injection may change as more studies are published in the future.

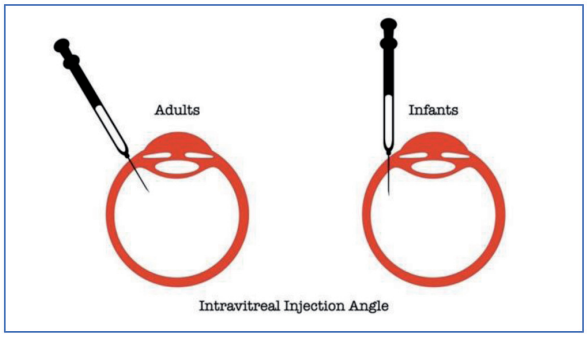

Figure 1. Angle of the needle during intravitreal injection among infants

F. Sterile 30-gauge 0.5 inch disposable needle on a 1 cc syringe or, when available, finer and shorter needle on a syringe with smaller capacity may be used for intravitreal injection of anti-VEGF agents. The needle must be inserted just deep enough to penetrate the sclera and enter the vitreous when performing the injection. At most, less than half the length of the 30-gauge needle should be inserted into the eye. It is essential to refrain from inserting the entire length of the needle into the eye to avoid hitting the retina.[29] Stabilize the hand by anchoring the middle finger to prevent the needle from going too deep just in case the infant moves. This also provides additional stability to the eyeball and proprioceptive feedback to the surgeon. An appropriately sized cotton applicator or a sterile Flynn scleral depressor may be used to position the globe as needed. If the baby is restless and uncooperative, wait for a few minutes for the infant to settle down or give a pacifier.

G. When injecting the anti-VEGF agent, avoid injecting with undue intensity that may cause a retinal injury from the jet stream produced by injection.

H. After the injection and the needle is withdrawn, the ophthalmologist may apply a sterile cotton applicator to prevent reflux of liquid vitreous.

I. Whenever possible, the ophthalmologist should assess lens clarity, central retinal artery and optic nerve perfusion by checking for venous pulsation, and presence of retinal breaks via indirect ophthalmoscopy.

J. Anterior chamber paracentesis may be promptly performed in cases that show a sustained rise in intraocular pressure.

K. Bilateral same day injections:[16,25]
   1. Each eye should be prepared with povidone-iodine separately.
   2. A completely new and different surgical set of lid speculum, instruments, 30-gauge needle and syringe should be utilized.
   3. Whenever feasible, separate vials of medication with different lot numbers should be used for each eye. Record the

lot numbers in the operative record.

L. There is no robust evidence to suggest that the instillation of post-injection antibiotics provides additional benefit in reducing the risk of intraocular infection after intravitreal injections.[16,30,31]

VI. Post-Injection Management

A. Post-injection follow-up is advised within 7 days then monitor the status of ROP as necessary.

B. Parents should be instructed to bring the infant sooner for follow-up if with signs of inflammation or infection.

This consensus statement is subject to reevaluation and revision as new evidence-based studies on intravitreal anti-VEGF injections among infants become published and new practice patterns evolve.

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