Original Article

Intravitreal Antivascular Endothelial Growth Factors for Retinopathy of Prematurity in Ibadan: Method of Administration

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Abstract

Purpose: To outline the method of administration of intravitreal antivascular endothelial growth factor (anti-VEGF) for retinopathy of prematurity (ROP) for the purpose of improved eye care among neonates. **Background:** ROP is a major potential, but largely preventable cause of blindness in the pediatric population. ROP has been shown to be a two-stage event with an initial disruption to normal retinal vessel growth, which is then accompanied by the second stage of vessel development. Preterm infants have undeveloped retinas, with avascular areas at the periphery. Subsequently, as the infant grows, these undeveloped retinas lacking an adequate supply of oxygen then stimulate angiogenic factors for the development of new vessels. Some predisposing risk factors include inappropriate oxygen therapy and lower birth weights. Initially, ROP was documented to be sporadic in most regions of Africa, but due to the recent advancement in medical facilities and personnel training, more preterm babies are surviving, thereby increasing the rate of ROP. Our hospital, the University College Hospital, Ibadan, has been assessing preterm babies for signs of ROP in conjunction with the neonatologists for the last four years, with various stages of ROP being diagnosed and treated. Intravitreal use of anti-VEGF has been accepted as a valuable therapy in preventing the development of advanced cases of ROP. The purpose of this study is to describe the method of administration of this important medication. **Conclusion:** Intravitreal anti-VEGF may prevent avoidable blindness in babies with ROP. However, to prevent devastating complications, appropriate techniques and the guidelines given in this study should be considered to minimize complications.

Keywords: Antivascular endothelial growth factor, methods of administration, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP), an ischemia-induced retinopathy, is the most common ophthalmic condition linked with premature birth[1] and remains a significant contributor to childhood blindness globally[2] and an incipient cause in developing nations.[3,4]

ROP was first termed retrolental fibroplasia (RLF) in 1942 by Terry.[5] By the early 1950s, hyperoxia was implicated in the growing incidence of RLF. With a seemingly better knowledge of ROP two decades later, an effort at treatment was attempted. However, concerns such as lack of an appropriate classification system made the results unimpressive.[6] By 1984, the publication of an appropriate classification system[7] upgraded the management of ROP.

Routine screening of preterm babies was not the norm due to limitations or lack of screening facilities, skilled workforce, and nonavailability of treatment modalities.[8,9] Recent reports in various parts of Africa show an increasing trend in the screening and detection rate of ROP.[10,11] Various studies carried out locally in Nigeria have also revealed increasing rates of screening and diagnosis of ROP.[12-14] Furthermore, increasing access to specialized neonatal care units and an upsurge in the uptake of assisted conception especially *in vitro* fertilization have been associated with preterm babies' survival. Some of the documented risk factors for ROP include prematurity which predisposes to conditions such as sepsis and respiratory distress, for which supplemental oxygen is

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utilized in the management. This supplemental oxygen if not well regulated is an established association of ROP.

The ROP Team at the University College Hospital, Ibadan, has been screening babies for ROP for the past four years. From these screenings, babies with various stages of ROP have been being diagnosed and treated [Figure 1].

The current treatment modalities for ROP are dependent on indications for treatment. Type 1 ROP is treated while Type 2 is observed closely.[15] The treatment of ROP is dependent on the stage or zone of presentation and may include retinal laser photocoagulation, injection of antivascular endothelial growth factor (anti-VEGF) (bevacizumab/ranibizumab), or pars plana vitrectomy.[16-19]

Anti-VEGF therapy for ROP was primarily considered after earlier studies[20-22] recognized VEGF as an important mediator in the vasoproliferative-ROP-pathway. Furthermore, the superiority of bevacizumab over other treatment options was restated by the multicenter clinical trial; Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP).[23]

Modalities of treatment in our hospital, depending on the stage at diagnosis include intravitreal bevacizumab and retinal laser therapy. Our choice of bevacizumab is because it is much cheaper than ranibizumab and a single vial can be used for multiple injections under strict asepsis. It has been proven that bevacizumab may be more efficacious than ranibizumab in ROP with fewer chances of recurrence and lower probability of repeat intravitreal injections.[24] The BEAT-ROP study showed fewer recurrences of posterior ROP with intravitreal bevacizumab and also lesser complications when compared to laser therapy.[23]

An advantage of intravitreal bevacizumab is the fact that it is a brief procedure in comparison to laser photocoagulation and hence less stressful for the neonate. Due to the brevity of the procedure, it may be used to treat very ill babies who otherwise may not be able to withstand the stress of laser photocoagulation. Other advantages of anti-VEGF injections include its ability to avoid retina scars and scotomas associated with laser pan-retinal photocoagulation. Laser photocoagulation also induces the progression of myopia, which is not seen with anti-VEGF.[23]

Despite the benefits of anti-VEGF, possible disadvantages include the possible development of endophthalmitis and retinal detachment.[25] Other reported adverse events are optic atrophy, retinal breaks, macula hole, and retinal pigment epithelial (RPE)/choroidal rupture.[26,27]

Though existing literature have reported low rate of complications,[28] infants receiving intravitreal anti-VEGF should be followed up closely for prompt diagnosis of vision-threatening events.

Figure 1: Retinopathy of prematurity in Ibadan

Method of Administration of Intravitreal Antivascular Endothelial Growth Factor in a Neonate with Retinopathy of Prematurity

Recommended antivascular endothelial growth factor agents

- Ranibizumab (dose 0.25 mg in 0.025 ml) – Half of adult dose[29]
- Bevacizumab (dose 0.625 mg in 0.025 ml) – Half of adult dose.[23,29]

Indications for intravitreal antivascular endothelial growth factor

- Zone I ROP: Any stage with plus disease
- Zone I ROP: Stage 3 – No plus disease
- Zone II ROP: Stage 2 or stage 3 with plus disease
- Aggressive posterior ROP
- Zone III babies with type 1 ROP not fit for laser photocoagulation (hazy media).

Preoperative preparation

- Neonates must have been certified fit for intravitreal injection by managing neonatology team
- Preferable to give the intravitreal injection in the operating theater. Occasionally, it can be given in the neonatal unit, but total asepsis must be maintained as would obtain in theater
- Intravitreal injection is taken from a new, unopened bottle of Avastin
- Neonates with ROP given priority; usually first on the operating list when other patients are scheduled for anti-VEGF therapy.

Procedure

- The neonatal team must certify the neonate fit for the injection by the absence of apnea and fever. The vital signs must be stable and continuously monitored with a pulse oximeter. The neonatal team including a doctor and nurse are always present to monitor the baby, while the injection is being administered in our center. Our operating theater is on the same floor and directly opposite the neonatal ward, so providing easy access
- Neonates are positioned on the operating table and monitored by an assistant [Figure 2]
- A small headrest or doughnut is made to support the head
- Topical anesthesia with instillation of one drop of tetracaine hydrochloride every 5 min for 15 min prior to injection being given

- Surgeon and scrub nurse are fully scrubbed and gowned with face masks
- Procedure is under total asepsis
- Intravitreal injection preparation – Intravitreal bevacizumab is drawn into an insulin syringe usually 1.25 mg in 0.05 ml with the aim of giving half (0.625 mg in 0.025 ml) under aseptic condition
- The bevacizumab injection for each patient is usually prepared and withdrawn into the insulin syringes from the bevacizumab vial by a scrubbed assistant to prevent any form of contamination or infection if more than one patient is to be injected
- A new 27-G needle is then placed on the tip of the insulin syringe with the bevacizumab injection placed on the sterile trolley for each patient
- If bilateral intravitreal bevacizumab injections are to be given, a separate tray with different instruments is prepared for each eye
- The periocular area is cleaned with a sterile 5% povidone iodine-soaked gauze mounted on a cleaning forceps in an inward to outward motion. There after, the pediatric sterile drape is placed over the sterile field exposing only the eye of regard
- If both eyes are affected and to be injected with intravitreal bevacizumab, cleaning and draping is done individually for each eye by the scrub nurse
- Lid speculum is introduced to retract the lids
- 5% povidone iodine is instilled in the eye and irrigated after 30 seconds
- An assistant is needed to stabilize the neonate's head to prevent any sudden movements [Figure 2]
- The site of injection is identified; usually in the inferotemporal quadrant but may vary depending on the quadrant with better scleral exposure for measurement
- A pair of calipers is used to measure the site of injection usually 1.5 mm from the limbus to avoid the lens being damaged; the distance may vary in bigger babies [Table 1][30,31]
- The surgeon then expresses the excess drug to have 0.625 mg in 0.025 ml in the syringe
- The 27-G needle is introduced into the eye at 1.5 mm from the limbus toward the direction of the optic nerve head bevel up [Figure 2]
- 0.625 mg in 0.025 ml of bevacizumab is injected intravitreally
- The needle is then gently withdrawn and a cotton tip soaked in povidone iodine is placed over the entry point of the injection [Figure 2]
- The intraocular pressure is checked digitally; if the globe is tense, a gentle paracentesis may be done with a 27-G needle at 3 or 9 o'clock depending on the eye
- 5% povidone iodine is then instilled
- Antibiotic drop moxifloxacin is instilled
- The lid speculum is removed and the eye covered briefly with a sterile gauze and removed

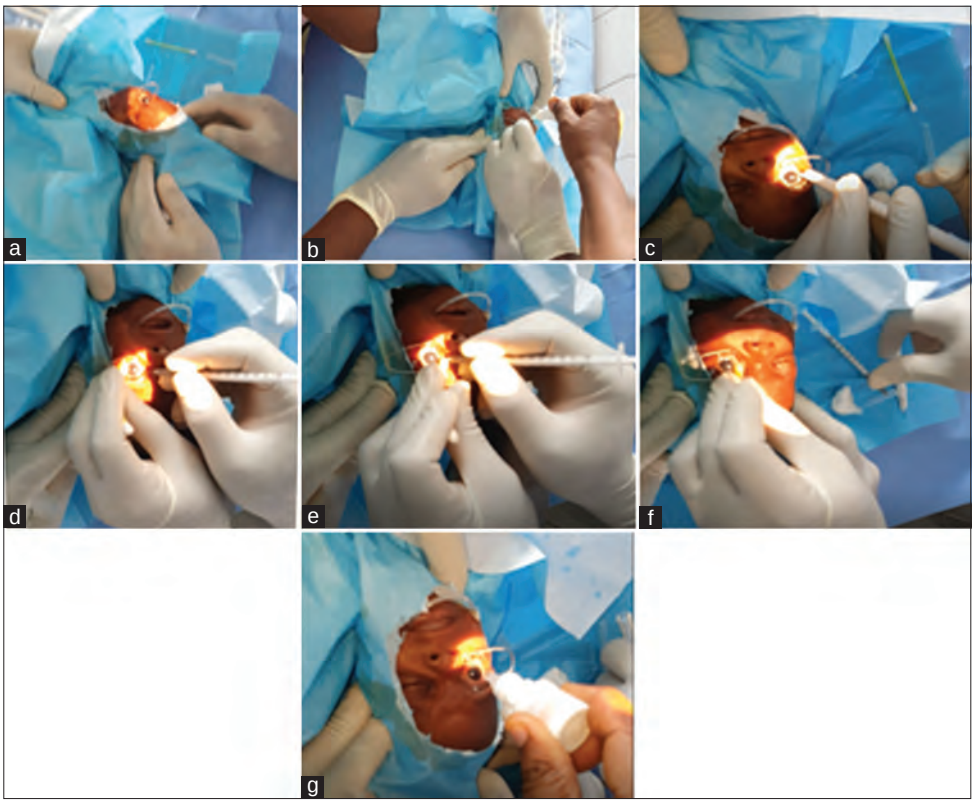

Figure 2: (a) Cleaning, draping, speculum placement, and head stabilization by the assistant; (b) preinjection antibiotic instillation; (c) calipers to measure 1.5 mm from the limbus; (d) injection of anti-VEGF; (e and f) tamponade with cotton bud to prevent reflux and vitreous incarceration; (g) postinjection antibiotic

- The eye should not be padded
- Hourly instillation of moxifloxacin eyedrops is advised postoperatively before bedtime.

Postoperative care

- Patients are monitored on the ward by the neonatologists for apnea with a close watch on the vital signs and oxygen saturation depending on neonates' health
- Hourly instillation of moxifloxacin eye drops for the first 24 h
- Neonates are reviewed at the neonatal care unit about 6 h postoperatively; the eye is examined for any signs of undue inflammation and the state of health of the neonate. Intraocular pressure is tested digitally or with Icare Tonometer in suspicious cases. Most times, intraocular pressure is low following paracentesis
- Neonates are also reviewed 24 h postinjection with careful examination of the anterior segment looking for corneal edema, anterior chamber reaction, or fibrin. Binocular indirect ophthalmoscopy is done to exclude vitreous inflammation and endophthalmitis
- Topical antibiotic is continued for a week and examined again 1 week postinjection
- Other management is continued by the neonatologists.

Follow-up visits

- Patients are reviewed 1 week postinjection for dilated binocular ophthalmoscopy; the retina is examined and signs of regression or new findings are noted and documented
- Patients are then seen every 2 weeks for a month and then monthly until regression and maturation of retinal vessels
- Patients will then be referred for review by the pediatric ophthalmologists for follow-up care
- Pediatric ophthalmologists are important in managing any sequelae of ROP such as myopia and glaucoma.

Discussion

ROP screening was commenced at the University College Hospital, Ibadan, in 2017. We have screened more than 250 neonates, out of which we have treated 10 neonates with laser photocoagulation and given intravitreal bevacizumab to 13 eyes.[32]

The most important consideration is the accurate localization of the injection site in premature babies.

The surgeon must be conversant with the following anatomical landmarks [Figure 3].[30] The peculiarities of the premature and neonatal eye should be considered before administration of intravitreal injections.

Based on these peculiarities, Table 1 is proposed, which indicates that a distance of 1.5 mm should be used for babies below 6 months of age.

Previous studies suggest that the site of injection should avoid damage to the ciliary body, retina and the lens in babies below 6 months of age. An average of 1.5 mm distance from the limbus is advised. This will avoid damage to the retina, ciliary body, and the lens.[30]

The standard precautions taken for adult patients need to be followed as the development of intraocular infection is devastating for a neonate and may lead to the loss of the eye more rapidly.

The intravitreal injection is given in the operating theater of the University College Hospital, Ibadan, under aseptic conditions. We also use an operating microscope to accurately localize the site of injection. Povidone iodine 5% is used for both the eyelid skin and the conjunctiva sac and irrigated subsequently to avoid sensitivity.

A neonatal speculum is used and is specific because of the size of the eye.

Topical anesthesia with tetracaine hydrochloride is used with caution to avoid cornea edema.[33]

The calipers must be accurate, and the adjustment must be checked before use.

A 27-G needle with a 1-ml syringe is advised. A little more than the required dose of anti-VEGF is withdrawn into the syringe. Thereafter, air in the syringe and the injecting needle is carefully expelled until a drop of the drug is noticed at the tip of the needle, while simultaneously ensuring the mark on the insulin syringe is set at 0.025 ml.

After injecting the drug, a sterile cotton bud is placed over the site to prevent reflux of the drug and vitreous incarceration.

Paracentesis is done after the injection to reduce the intraocular pressure. The anterior chamber of the neonate is shallow; therefore, the paracentesis with a 27-G or 30-G needle is done by entering the anterior chamber perpendicularly and parallel to the iris. This will avoid damage to the iris or lens. It is also better not to dilate the pupil before the procedure. This will protect the lens.

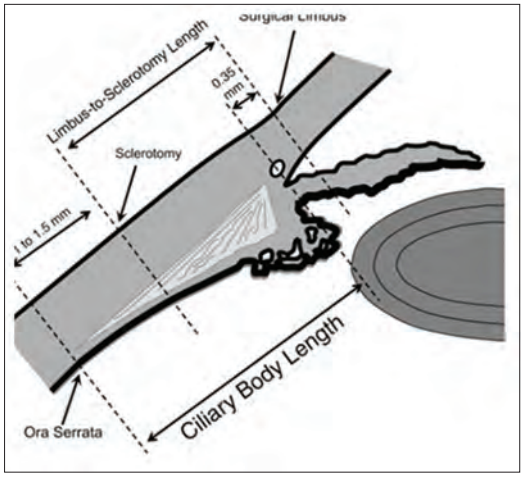

Figure 3: Anatomical landmarks for sclerotomy in the pediatric population

Table 1: Sclerotomy for pediatric population

Age	Ciliary body length (mm)	Limbus to ora (mm)	Calculated limbus to sclerotomy (mm)	Applied limbus to sclerotomy (mm)
0-6 months	2.6	2.95	1.45	1.5
6-12 months	2.86	3.21	1.71	2.0
1-2 years	3.28	3.63	2.13	2.5
2-3 years	3.75	4.10	2.60	3.0
Adults	4.60	4.95	3.45	3.5/4

Postoperative use of topical antibiotics is advised. The eye should not be padded to prevent amblyopia.

Babies are reviewed 6 hours and 24 hours after the injection for signs of endophthalmitis.

Pediatric ophthalmology follow up is mandatory to detect other ocular complications of prematurity. Pediatricians also need to follow up with the babies for systemic complications.[34,35]

Conclusion

Intravitreal anti-VEGF may prevent avoidable blindness in babies with ROP. However, the adverse effects of the procedure can be devastating. Appropriate techniques and the guidelines given in this study should be considered to minimize complications.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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