SAFER-ROP: Updated Protocol for Anti-VEGF Injections for Retinopathy of Prematurity

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BACKGROUND AND OBJECTIVE: To describe a safe and dependable protocol for intravitreal injections for the treatment of retinopathy of prematurity (ROP).

MATERIALS AND METHODS: SAFER is an acronym used to describe the injection protocol and includes (S)hort needle (4-mm length), (A)ntiseptic/antibiotic (5% to 10% topical betadine), (F)ollow-up (48 to 72 hours post-injection), (E)xtra attention to detail (clean environment, injection site 0.75 mm to 1.0 mm posterior to limbus), and (R)echeck (1 to 2 weeks following injection and until mature vascularization or laser).

RESULTS: No cases of cataract formation, endophthalmitis, or vitreous hemorrhage using this technique were reported in a recent retrospective chart review.

CONCLUSION: This protocol is a safe way to inject anti-vascular endothelial growth factor and to monitor ROP progression following injection.


INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading, yet treatable causes of childhood blindness in both the United States and worldwide. Its incidence is only increasing as medical advances have continued to push the age of viability to 21 weeks postmenstrual age. Although laser remains the conventional treatment standard, the use of anti-vascular endothelial growth factor (VEGF) drugs, including bevacizumab (Avastin; Genentech, South San Francisco, CA) and ranibizumab (Lucentis; Genentech, South San Francisco, CA) have demonstrated promising and improved visual outcomes with subsequent increased use. Despite improved structural outcomes from utilizing anti-VEGF drugs, complications induced by needle insertion technique include but are not limited to injury to and displacement of the crystalline lens, retina resulting in retinal tears, detachments, or even scleral perforations and endophthalmitis.

There have been many published standardized intravitreal injection techniques for adults to ensure safe and reproducible delivery. However, standardized techniques for anti-VEGF administration in ROP are lacking. For example, the BEAT-ROP study, which was the first controlled study...
comparing intravitreal bevacizumab to laser treatment, used a 31-gauge 7.93-mm needle for anti-VEGF delivery. The prospective RAINBOW study comparing ranizumab to laser treatment, on the other hand, used a 30-gauge 1/2-inch (12.7-mm) needle. The recently published study by Wright et al. used a 32-gauge 4-mm needle (TSK SteriJect; Air-Tite Products, Virginia Beach, VA) and was the first published technique to standardize guidelines for intravitreal injections in ROP. They demonstrated, with use of pathological specimens, how standard 12-mm-long needles could penetrate the lens or retina upon injection. In contrast, the 4-mm length needle was able to effectively penetrate into the vitreous cavity without damaging the lens or retina. A retrospective chart review investigating the safety of this technique by Austin Retina Associates and Bascom Palmer Eye Institute, revealed no cases of cataract formation, endophthalmitis, vitreous hemorrhage, or corneal infection. In this paper, we expand upon this technique and propose the first published ROP treatment protocol entitled SAFER-ROP in order to deliver effective treatment while minimizing avoidable complications.

**S: Short Needle**

✓ 32-gauge 4.0-mm TSK SteriJect needle

**A: Antiseptic/Antibiotic**

✓ Betadine 5% or 10% both before and after treatment

**F: Follow-Up**

✓ 2 to 7 days post-injection to examine for injection complications

**E: Extra Attention to Detail**

✓ Maintain clean environment (gloves, masks, single-use caliper, and eyelid speculum)
✓ Assess for conjunctivitis and nasolacrimal duct obstruction prior to injection
✓ Determination of safe injection site 0.75 to 1.0 mm posterior to limbus using the ora nonogram

**R: Recheck**

✓ 1 to 2 weeks following injection and until mature vascularization is complete
✓ Use fluorescein angiogram for all treated patients between 60 to 65 weeks postmenstrual age if not vascularized
✓ Laser avascular areas if necessary

**Figure 1. SAFER protocol checklist.**

**MATERIALS AND METHODS**

SAFER is an acronym used to describe the injection protocol (Figure 1), which consists of the following: (S)hort needle, (A)ntiseptic/antibiotic, (F)ollow-up, (E)xtra attention to detail, and (R)echeck every 1 to 2 weeks post-injection until complete retinal vascularization or additional laser has been administered to avascular retina. The “short needle” is a 32-gauge, thin-walled, stainless steel hypodermic needle 4 mm in length. The “antiseptic/antibiotic” utilized is topical 5% or 10% betadine. It is instilled before and after the injection. “Follow-up” should be performed 48 to 72 hours post-injection to rule out endophthalmitis. “Extra attention to detail” includes use of the ora nomogram to determine the safest injection distance from the limbus in each quadrant, clean instruments, gloves, and masks for all involved in the injection, including nurses or respiratory therapists holding the baby. Additional attention should focus on risk factors for endophthalmitis by assessing the patient for the presence of nasolacrimal duct obstruction and conjunctivitis. It is common in the neonatal intensive care unit (NICU) for the team to have already started topical antibiotics for mild discharge...
without consulting ophthalmology. Also, in patients on continuous positive airway pressure (CPAP) ventilation, contaminated air from the nasopharynx may be blowing under the mask onto the injection field. The authors often find that long nasal prongs can easily and safely be inserted by NICU team for the short time it takes to inject to prevent contamination of the field. Furthermore, unsheathed needles should not be held near the infant’s CPAP, nose, or mouth while maneuvering into position for an injection. When teaching this technique, it may be best to ensure trainees hold the syringe in one hand and to use the other hand to depress the plunger. This way, the plunger is not accidentally depressed outside the eye as “pushing the needle in through sclera” and, hence, reducing drug dose in the vitreous. Additionally, there is less chance of inadvertent change in needle direction as they try to reach the plunger with fingers of the hand also holding the syringe.

Recheck the patient every 1 to 2 weeks following anti-VEGF treatment. We also recommend considering performing a fluorescein angiogram for all treated patients by 60 and 65 weeks postmenstrual age, if not already vascularized into Zone III, with a view to treat with additional laser if necessary. This is important because although about 18% of eyes treated with anti-VEGF vascularized to zone III by three months post-injection, and at least 61% vascularized by 2.5 years, a significant number of infants do not fully vascularize their retina following intravitreal anti-VEGF injections. ROP recurrence following anti-VEGF injection may occur up to 5 years later.

The following is a description of how the injections are performed (Video available at www.Healio.com/OSLRetina). Injections are performed at the bedside in the neonatal intensive care unit on awake infants. Topical anesthetic is instilled into the eye followed by the placement of a sterile eyelid speculum. The use of additional sedation or anesthesia is up to the discretion of the neonatologist but has not been found to affect adverse outcomes. Betadine 5% to 10% drops are then instilled. Calipers are used to measure and mark the location for the injection at 0.75 mm to 1.0 mm posterior to the temporal limbus using the ora nonogram. The medication is injected using the 4-mm, 32-gauge needle as evidenced by no cases of cataract, endophthalmitis, vitreous hemorrhage, or corneal infection with 220 infants enrolled in the study.

**RESULTS**

Both Austin Retina Associates and Bascom Palmer Eye Institute safely performed this technique employing the 4-mm, 32-gauge needle as evidenced by no cases of cataract, endophthalmitis, vitreous hemorrhage, or corneal infection with 220 infants enrolled in the study.

**DISCUSSION**

The increasing frequency of intravitreal anti-VEGF use for the treatment of type 1 ROP following the publication of the BEAT-ROP and RAINBOW trials necessitates a practical protocol for both the actual injection and follow-up for these patients. In the RAINBOW trial, of the 302 eyes that were injected with either 0.1 mg or 0.2 mg ranibizumab, two cases of endophthalmitis and one case of cataract development were reported. In addition, a case of endophthalmitis following anti-VEGF injection in a neonate was recently reported. Although, these complications are exceedingly rare, the visual consequences can be devastating for the baby. As we continue to push the upper limit of survival in lower birth weight and gestational age infants, the numbers of treatable ROP and frequency of injections will rise with a corresponding increase in the number of complications. Many ROP patients suffer from other medical conditions or may be immunocompromised, further necessitating a standardized protocol in order to minimize possible sight and life-threatening complications. In addition, no “formal training” is required in order to inject anti-VEGF, education is critical to creating the safest algorithm possible. Contrary to minimal follow-up after injection, as in the BEATROP, we recommend a thorough protocol.

We have therefore formalized an injection and follow-up protocol to guide clinicians in order to optimize the safety of anti-VEGF treatment in ROP. In the SAFER algorithm:

The (S)hort needle is a 32-gauge, 4-mm needle that cannot penetrate the retina on the opposite side and if aimed posteriorly cannot penetrate the lens. In contrast, other studies have referenced a needle that is 8-mm or longer and could penetrate either.

The (A)ntiseptic/antibiotic: Although several published studies discuss the importance of “sterile prep,” these studies do not specifically discuss the concentration of betadine used and the importance of this. We use 10% povidone-iodine without sequelae as demonstrated in a recent study of 124 eyes. In this study there were no adverse events, including endophthalmitis, keratitis, cataract, vitreous hemorrhage, or retinal detachments. One critical point to keep in mind is that neonatal intensive care units (NICUs) are commonly contaminated with pathologic bacteria. Since neonates are considered to be immunosuppressed, they are more susceptible to infection. The
use of 10% povidone-iodine carries more antiseptic properties than the typical 5% povidone-iodine commonly used for intravitreal injections. In addition to implementing the use of 10% povidone-iodine prior to injection with this protocol, a drop of 10% povidone-iodine is instilled immediately following the injection as well. Also, a combination antibiotic-steroid drop is given following the second povidone-iodine drop in order to quell any irritation that may arise.

The (F)ollow-up: In adult patients, after an intra-vitreal injection, the normal follow-up period is 4 to 6 weeks. However, when the patient leaves the office following the injection, they are asked to be aware of symptoms including severe and constant pain, worsening pain after the first day, significant decrease in vision, severe increase in floaters, or a curtain or veil in the visual field. If the patient calls with these symptoms, they are examined by the physician on-call as soon as possible. In contrast, neonates cannot report these subjective symptoms that correlate with objective findings. Although the neonatologists on staff are observing for clinical signs of infection such as fever and conjunctival and lid swelling, by the time the infection is discovered it is often too late in the course of an infection for adequate rescue. Therefore, we advocate a dilated examination 48 to 72 hours after each injection to assess for post-injection complications. If signs of endophthalmitis or other complications are present, then treatment can be initiated immediately.

The (E)xtra attention to detail: We advocate a sterile set-up in the NICU for all injections. This includes strict hand washing without touching the sink handle and gloving immediately after and between each exam. The binocular indirect ophthalmoscope should be positioned for examination prior to hand washing. The use of operating room scrub hats, masks, clean/ single-use instruments, a separate set of gloves for each patient, and the use of the “no-touch technique,” in which the ophthalmic lens and calcium alginate swab/scleral depressor are picked up once from a sterile setting and put down only once the examination is complete, are specifically enacted to obviate any transmission of bacteria to these immunosuppressed neonates.

It is important to exclude possible risk factors for endophthalmitis before performing any intraocular procedure. Congenital nasolacrimal duct obstruction is commonly present in premature infants and is directly related to the degree of prematurity. It is important to press on the nasolacrimal sac and ensure there is no reflux of material when planning anti-VEGF injection and assess risk factors appropriately. It is particularly important to enquire about infections and review the chart and drug history as most “milder” infections are treated by the neonatology team without the need for an ophthalmology consult. Hence the ROP team may never be aware of this risk factor.

We inject 0.75 mm to 1.0 mm from the limbus. Postmortem studies have shown that the pars plicata at the average age of injection (35 to 36 weeks PMA) is at this location. In the BEATROP study, it was advocated that the injections should be done at 2.5 mm. However, this distance is through the retina in the neonate and may predispose to vitreous hemorrhage or worse, retinal detachment secondary to the traction created by the vitreous plugging the hole. We measure carefully with a sterile caliper and inject parallel to the optic nerve using the 32-gauge, 4-mm needle.

(R)echeck: In the BEAT-ROP study, the endpoint was noted to be retinal vessel maturity based on the examination by the authors. However, we now know that many eyes that have been injected with anti-VEGF remain avascular. Recent evidence in the RAINBOW trial showed that even at the 0.2 mg dose of ranibizumab, recurrence occurs in approximately 20% of patients. This necessitates careful observation every 1 to 2 weeks following injection. Direct fundus exams in neonates, especially as they mature and become more difficult to restrain, can be extraordinarily difficult. Also, the difference between vascular and avascular retina is extremely difficult to ascertain, even amongst the most experienced examiners.

The question of how long babies need to be observed is influenced by many factors including the ability to keep neonates under close observation especially after they have been discharged from the treating ophthalmologist’s NICU. Yonekawa et al. reported 25 eyes which developed late retinal detachments following anti-VEGF treatments. Drenser et al. demonstrated that 7.5% of patients with ROP carry the familial exudative vitreoretinopathy (FEVR) gene, which may predispose these patient populations to recurrence due to the vascular nature of FEVR. Therefore, close follow-up is mandatory for all anti-VEGF treated infants until they are vascularized or vascularization has arrested in Zone 2; at which time laser photocoagulation to the avascular periphery should be considered. Therefore, our general rule is to recheck every 1 to 2 weeks post-injection and by 60 to 65 weeks, perform a fluorescein angiography and laser with pan photocoagulation the remaining avascular periphery as appropriate.

In conclusion, the use of a shorter needle in a sterile environment enhances the likelihood of safe drug delivery, but the actual injection is not the only important aspect of the process. Attention to detail and close follow-up are mandatory in order
to monitor and treat for infection and to ensure mature vascularization has occurred. Laser should be subsequently performed if vascularization has not occurred by the expected time course. Furthermore, the use of fluorescein angiograms following injections should be considered, given the prevalence of avascularity following treatment. With the implementation of SAFER-ROP, we hope to minimize the complications that can occur with intravitreal injection for ROP.

REFERENCES


