Practical guidelines for screening and treatment of retinopathy of prematurity in Saudi Arabia

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Abstract

Retinopathy of Prematurity (ROP) is one of the leading causes of bilateral blindness in childhood. Early detection and effective treatment can prevent blindness. Efficient and timely screening examination of the retina by an experienced ophthalmologist who deals with preterm neonates with ROP is the mainstay in the management of this disease. All neonatologists and pediatricians who care for these at-risk preterm neonates should also be aware of this timing. This practical guideline intends to provide guidance to ophthalmologists, neonatologists and allied health care professionals in Saudi Arabia on current indications for screening and management of retinopathy of prematurity to prevent or minimize subsequent complications. This practical guideline was led by the National Eye Health Program (NEHP) and Neonatology Services Improvement Program at Ministry of Health (MOH), furthermore it has been solicited and endorsed from both Saudi Ophthalmological Society (SOS) and Saudi Neonatology Society (SNS).

Keywords: Retinopathy of prematurity, Screening, Laser treatment, Anti-VEGF intravitreal injections

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Introduction

Retinopathy of Prematurity (ROP) is a proliferative disorder of the developing retinal blood vessels in preterm infants that potentially leads to blindness in a small but considerable percentage of these neonates. In term neonates, the retinal vasculature is fully developed, and ROP does not occur; however, in preterm neonates, the development of the retinal vasculature which proceeds from the optic nerve head anteriorly during the course of gestation, is incomplete, with the extent of the avascularity of the retina depending mainly on the degree of prematurity at birth. The multicenter trial of cryotherapy for retinopathy of prematurity (Cryo-ROP) proved the usefulness of peripheral retinal cryotherapy in reducing unfavorable outcomes. The follow-up report of the 10-year study confirmed that unfavorable structural outcomes were reduced from 48% to 27%, and unfavorable visual outcomes (ie, best corrected visual acuity worse than 20/200) were reduced from 62% to 44%. Laser photocoagulation has been used for peripheral retinal ablation with excellent success rates. Recently, the early treatment for retinopathy of prematurity...
randomized trial (ET-ROP) confirmed the effectiveness of treatment for severe ROP and redefined the indications for treatment.

To reduce the risk of visual loss, efficient and timely examination of the retina by an experienced Ophthalmologist who deals with preterm neonates with ROP is now the golden rule. All neonatologists and pediatricians who care for these at-risk preterm neonates should be aware of this timing.

The first published recommendations on screening of ROP in Saudi Arabia was published in 2003, after years of doing ROP screening. The goal of an effective screening program must be to identify the at-risk preterm neonates who require treatment for ROP to prevent blinding sequelae. It is also important to reduce the number of stressful examinations required for these sick neonates. Any screening program is liable to have over-referral or under-referral. Bearing all this in mind, the following guideline is being suggested. It is important to understand that there can be different screening standards in other world locations.

The objective of this document is to provide guidance to Saudi Arabia’s ophthalmologists, neonatologists, and allied health care professionals on current indications for screening and management of Retinopathy of Prematurity to minimize risk of blindness and maximize successful patient outcomes. These guidelines are not meant or intended to restrict improvement, nor to be a replacement for clinical judgment. Furthermore, these guidelines should not be used as a legal resource, as their general nature cannot provide individualized guidance for all patients in all circumstances. These guidelines do not attempt to comment on the financial impact of procedures recommended.

Ideally, guidelines are flexible tools that are based on the best available scientific evidence and clinical information, reflect the consensus of professionals in the field, and allow physicians to use their individual judgment in managing their patients.

This Guideline has been developed after numerous meetings and discussions of the ROP Task Force Committee and after an ROP workshop with both International and local participants. The development of this Guideline, which was led by the National Eye Health Program (NEHP) at Ministry of Health (MOH), has been undertaken by a multidisciplinary guideline development group (GDG) of ophthalmologists, neonatologists, and Information Technologists Experts. The Guideline will be revised periodically.

Recommendations

Screening

Inclusion criteria

- Neonates with birth weight of 1500 g or less and/or gestational age of 32 weeks or less (as defined by the attending Neonatologist).
- Preterm neonates (≤36 weeks) receiving supplemental O₂ for 50 days or more.
- Special attention should be paid to larger preterm neonates at risk of ROP who receive frequent RBC transfusions or exchange transfusions to treat anemia of prematurity or Rh hemolytic disease of the newborn.

Examination

The screening examination can be stressful for both babies and parents. The examination requires a well-dilated pupil so the peripheral retina can be fully visualized.

- Ophthalmological notes should be made after each ROP examination, detailing zone, stage, and extent in term of clock hours of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination (if any) and be kept in the baby’s medical record.
- Effort should be made to minimize the discomfort and systemic effect of this examination by pretreatment of the eyes with topical anesthetic agent. Pacifiers or oral sucrose, etc, can also be used.
- Pupil dilatation is done by using phenylephrine 2.5% and tropicamide 1% eye drops x 2, 15 min apart, instilled 1 h before examination.
- Retinal examination should be done using lid speculum and scleral rotator/depressor specified for neonates.
- Retinal screening examinations performed after pupillary dilation using binocular indirect ophthalmoscopic examination or using wide-angle retinal digital photography to detect ROP.
- Retinal examinations by indirect ophthalmoscope in preterm neonates and interpretation of fundus photography should be performed by an Ophthalmologist who has enough knowledge and experience to enable accurate identification of the location and extent of retinal changes of ROP.
- The “International Classification of Retinopathy of Prematurity Revisited” should be used to classify, draw and record these retinal findings at the time of examination.
- Acute-phase of ROP screening should be based on the neonate’s age. The onset of serious ROP correlates better with postmenstrual age (gestational age at birth plus chronological age) than with postnatal age. That is, the youngest infants at birth take the longest time to develop serious ROP. Previously, this knowledge has been timely used in conducting a screening schedule. This schedule provides a system for detecting ROP potentially damaging to the retina with 99% confidence.
- All babies <32 weeks’ gestation age or birth weight <1500 g should have their first ROP screening examination prior to discharge.
- Where a decision is made not to screen a baby, the reasons for doing so should be clearly stated in the baby’s medical record and the examination should be rescheduled within one week of the intended examination.

Timing of first examination

- Any preterm neonate of gestational age of 27 weeks or less should have the first fundus examination at postmenstrual age of 31 weeks.
- Any preterm neonate of gestational age of 28 weeks or more should have the first fundus examination at 4–6 weeks chronological (postnatal) age.
- Any eligible stable preterm neonate planned for discharge prior to the scheduled fundus examination should have the first fundus examination at the time of discharge.
Follow-up examinations

Follow-up examinations should be recommended by the examining Ophthalmologist on the basis of retinal findings classified according to the International Classification. The following schedule is suggested:

- One week or less follow-up if Stage 1 or 2 ROP in zone I (without Plus Disease) or Stage 3 ROP in zone II (without Plus Disease).
- One to two weeks follow-up in case of immature vascularization in zone I with no ROP, Stage 2 ROP in zone II or Regressing ROP in zone I.
- Two weeks follow-up in case of Stage I ROP in zone II or Regressing ROP in zone II.
- Two to three weeks follow-up in case of Immature vascularization in zone II with no ROP, Stage 1 or 2 ROP in zone III or Regressing ROP in zone III

Findings suggesting that follow-up examinations can be reduced more than Three weeks include the following:

- Zone III retinal vascularization attained without previous zone I or II ROP (if there is a doubt about the zone or if the postmenstrual age is less than 35 weeks, confirmatory examinations may be warranted).
- Postmenstrual age of 45 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present.
- Regression of ROP (care must be taken to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression).

The presence of Plus Disease (defined as dilation and tortuosity of the posterior retinal blood vessels) in zone I or II suggests that peripheral ablation, rather than observation is suitable.18

Termination of ROP screening

Screening can be stopped when the baby is no longer at risk of sight-threatening ROP.

- In babies who reached full retinal vascularization.
- In babies who never developed any ROP, the risk of sight-threatening ROP developing is minimal once the retinal vessels have reached zone III, which is unlikely to occur before 37 weeks postmenstrual age and a decision to stop screening before this age must be carefully evaluated.
- In babies developing ROP which does not meet the criteria for treatment, screening can be safely stopped when clear signs of active regression of ROP (includes regression of retinal vascular changes posterior to the ridge and normal blood vessels crossing the ridge into the avascular zone and entering the nasal serrata).
- In the presence of ROP, screening for progressive active disease may be discontinued when any of the following characteristics of regression are seen on at least in 2 successive examinations:
  - Partial resolution progressing towards complete resolution
  - Change in the color of the ridge from salmon pink to white
  - Transgression of vessels through the demarcation line
  - Commencement of the process of replacement of active ROP lesions by scar tissue

ROP treatment

Timely treatment for ROP is effective at preventing severe visual impairment. Treatment should be done in NICU Level-3 with deep sedation or in the operating room under general anesthesia.

- Retinal findings requiring ablative treatment should be given according to the early treatment for retinopathy of prematurity randomized trial study.7,10

Treatment may also be initiated for the following retinal findings:

- zone I ROP: any stage with plus disease
- zone I ROP: stage 3 – no plus disease
- zone II ROP: stage 2 or 3 with plus disease

Special care must be used in determining the zone of disease. The number of clock hours of disease may no longer be the determining factor in recommending ablative treatment. Treatment should generally be accomplished, when possible, within 72 h of determination of treatable disease to minimize the risk of retinal detachment.

- Babies with aggressive posterior ROP should be treated as soon as possible and preferably within 48 h. ROP requiring treatment but which is not aggressive posterior ROP should normally be treated within 48–72 h.
- Transpupillary diode laser therapy is recommended as the first line of treatment of ROP.
- Treatment with near-confluent laser burns should be administered to the entire avascular retina.
- The unavailability of diode laser equipment or the inability to transfer the preterm neonate to another center should not prevent or delay the treatment of ROP. In these situations, treatment with argon laser, cryotherapy, or intravitreal anti-VEGF may be completed by an Ophthalmologist experienced with these techniques.
- Solo treatment with antivascular endothelial growth factor (anti-VEGF) should only be done under research protocols. However, anti-VEGF therapy is a recent development in the treatment of ROP. In a randomized trial, intravitreal injection of bevacizumab, a recombinant humanized monoclonal antibody, was shown to be more effective than conventional laser therapy in decreasing the recurrence of zone I but not posterior zone II ROP.19

Post treatment review

Post-operative review is important to monitor disease regression and to determine if retreatment is necessary. This should be as follows:

- The first post-operative examination should take place 5–7 days after treatment and should be continued weekly for signs of decreasing activity and regression.
- Re-treatment or seeking another opinion should be done 10–14 days after initial treatment when there has been a failure of the ROP to regress.
● In anti-VEGF treated patients follow-up examination should continue for at least six months.

**Follow-up after screening or treatment**

After the acute phase, eyes that have reached stage 3 or have been treated should be monitored at a frequency dictated by the clinical condition to determine the sequelae. Any preterm neonate, even without ROP, should be examined at 6 months to 1 year of age for visual acuity testing, alignment check, and cyclopegic refraction.

**Parent information**

Communication with the parents by members of the staff is very important. Parents should be aware of ROP screening examinations and should be informed if their child has ROP, with subsequent updates on ROP progression. The possible consequences of serious ROP should be discussed at the time that a significant risk of poor visual outcome develops. Documentation of such conversations with parents in the nurse or physician notes is highly recommended.

**Organization of services**

Effective services for ROP screening and treatment with individual responsibilities must be the golden standard of any service delivery. Particular efforts must be focused to ensure that service delivery is appropriate for all those at risk, because there is a valid proof that babies transferred or discharged home before screening is complete are at risk of poor outcomes due to lack of adequate follow-up.

- Each NICU should have written protocols and must carefully define examination and follow-up of infants at risk of ROP according to these guidelines. Teamwork and collaboration between neonatologists, ophthalmologists, nurses, and photographers is for the best interest of these preterm neonates.
- These criteria should be recorded and should automatically prompt ophthalmological examinations.
- There should be a record of all babies who require review and the arrangements for their follow-up by an assigned ROP coordinator.
- If hospital discharge or transfer to another neonatal unit or hospital is considered before retinal maturation into zone III has taken place or if the neonate has been treated for ROP and is not yet fully regressed, the availability of appropriate follow-up ophthalmologic examination must be ensured, and specific arrangement for that examination must be made before such discharge or transfer occurs. The transferring primary neonatologist, after discussion with the examining ophthalmologist, should have the responsibility for communicating what examinations are needed and their required timing to the neonate’s new neonatologist. The new neonatologist should ascertain the current ocular examination status of the neonate from the record and through communication with the transferring neonatologist so that any necessary examinations by an ophthalmologist having experience in examination of preterm neonates for ROP can be arranged promptly at the receiving facility or on an outpatient basis if discharge is planned before the need for continued examination has ceased. All of this should be recorded in their transfer letter.
- If responsibility for arranging follow-up ophthalmologic care after discharge is delegated to the parents, they should be made to understand the likelihood of severe visual loss and blindness, and that there is a critical time window to be met if treatment is to be successful and that timely follow-up examination is essential for successful treatment. This information should preferably be communicated both verbally and in writing. If such arrangements for communication and follow-up after transfer or discharge cannot be made, the neonate should not be transferred or discharged until appropriate follow-up examination can be arranged by the unit that is discharging the neonate.
- Neonatologists/pediatricians and other practitioners who care for the neonates who have had ROP, regardless of whether or not they require treatment, should be aware that these neonates may be at risk of other seemingly unrelated visual disorders such as strabismus, amblyopia, cataract, etc. Ophthalmologic follow-up for these potential problems after discharge from the NICU is indicated.

**Conflict of interest**

The authors declared that there is no conflict of interest.

**References**

1. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol 1988;106:471–9.
2. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: ophthalmological outcomes at 10 years. Arch Ophthalmol 2001;119:1110–8.
3. McNamara JA, Tasman W, Brown GC, Federman LL. Laser photoagulation for stage 3+ retinopathy of prematurity. Ophthalmology 1991;98:576–80.
4. Hunter DG, Repka MX. Diode laser photoagulation for threshold retinopathy of prematurity: a randomized study. Ophthalmology 1993;100:238–44.
5. Laser ROP Study Group. Laser therapy for retinopathy of prematurity. Arch Ophthalmol 1994;112:154–6.
6. Iverson DA, Tresi MT, Orgel IK, Williams GA. Laser photoagulation for threshold retinopathy of prematurity. Arch Ophthalmol 1991;109:1342–3.
7. Amro Saleh AI, Ahmad Adil M, Abu El Asrar AM. Laser photoagulation for threshold retinopathy of prematurity. Saudi J Ophthalmol 1998;12:12–5.
8. Early treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121:1684–94.
9. Al-Amro SA, Al-Kharfi TM, Thabit AA, Al-Mofada SM. Retinopathy of prematurity at a university hospital in Riyadh, Saudi Arabia. Saudi Med J 2003;24:720–4.
10. Davis D, Goldman J, Palda VA. Handbook on clinical practice guidelines. Ottawa, Ont.: Canadian Medical Association; 2007.
11. Jacobsen PD. Transforming clinical practice guidelines into legislative mandates. Proceed with abundant caution. JAMA 2007;299:208–10.
12. Brooks SE, Marcus DM, Gillis D, et al. The effect of blood transfusion protocol on retinopathy of prematurity: a prospective, randomized study. Pediatrics 1999;104:514–8.
13. Saleh Al-Alaiyan, Khaled Saidy, Fahad Al-Hazzani. Retinopathy of prematurity in premature infants with severe rhesus hemolytic disease of the newborn. J Neonatal-Perinatal Med 2008;1:233–7.

14. International Committee of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123:991–9.

15. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. Ophthalmology 1991;98:1628–40.

16. LIGHT-ROP Cooperative Group. The design of the multicenter study of light reduction in retinopathy of prematurity (LIGHT-ROP). J Pediatr Ophthalmol Strabismus 1999;36:257–63.

17. Hutchinson AK, Saunders RA, O’Neil JW, Lovering A, Wilson ME. Timing of initial screening examination in retinopathy of prematurity. Arch Ophthalmol 1998;116:608–12.

18. Reynolds JD, Dobson V, Quinn GE, et al. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 2002;120:1470–6.

19. Mintz-Hittner HA, Kennedy KA, Chuang AZBEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New Engl J Med 2011;364:603–15.