Retinopathy of prematurity

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Abstract

Retinopathy of prematurity (ROP) occurs due to abnormal proliferation of retinal vessels. The most important risk factors which predispose to development of ROP include oxygen therapy, anemia needing blood transfusion, sepsis and apnea.Very low birth weight neonates, those born at ≤32 weeks of gestation and other preterm neonates with risk factors must be screened for ROP. As a general rule first screening should be done at 1 month of postnatal age. If screening detects ROP not needing treatment follow up should be planned according to location and stage of ROP. Better visual outcomes are observed with earlier treatment at lower threshold. Peripheral retinal ablation with diode laser under adequate analgesia and sedation is the preferred method for treatment of severe ROP. Guidelinesregarding the procedure of dilatation, ophthalmic examination and treatment (if required) have
been provided in the protocol. Close co-operation between the ophthalmologist and neonatologist
is essential for a successful management of ROP.

Key words : Prematurity , risk factors , retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina among premature babies. ROP begins to develop between 32 and 34 weeks after conception, regardless of gestational age at delivery and has two distinct phases.[1] During the acute first phase, the normal vasculogenesis of the retina is disturbed by the relative hyperoxia of the extrauterine environment. This causes vaso-obliteration and non-vascularization of some areas of the anterior retina.[2] The subsequent hypoxia causes a second chronic phase, characterized by the proliferation of vascular and glial cells arteriovenous shunt formation, occasionally leading to involution or permanent cicatricial changes and visual impairment.[3,4] In its more severe forms, it results in severe visual impairment or blindness, both of which carry a high financial cost for the community but also a high individual cost by affecting the normal motor, language, conceptual, and social development of the child.

Epidemiology

Studies from India reporting incidence of ROP provide interesting insights. Although screening criteria differ across different units and time-periods, overall incidence of ROP varies from 20% to 52% (Table 1) with more recent studies reporting lower rates of ROP ranging from 20% to 30%.[5-13] An important lesson is learnt from units reporting ROP in different time periods.[9] Initial low incidence of ROP rises with better screening protocols, availability of assisted ventilation services and survival of sicker, smaller neonates. In this phase even sick but relatively mature (late preterm) neonates have been reported to develop ROP. This period is followed by gradual decline in incidence of ROP especially of more severe variety.

Prematurity is the single most important risk factor responsible for retinopathy of prematurity. Incidence of ROP increases with decreasing gestation and birth weight. However, not all preterm neonates develop ROP. Important risk factors which increase the probability of developing ROP are oxygen therapy, anemia needing blood transfusion, sepsis and apnea.[5,7,9,11] Nevertheless, a very preterm extremely low birth weight neonate can develop ROP even without exposure to oxygen or presence of these risk factors.

In general more than 50% of preterm infants weighing less than 1250 g at birth show evidence of ROP and about 10% of the infants develop severe ROP.However, retinal detachment occurs and leads to

visual loss in only a few percent of infants with severe ROP, and in most cases, ROP regresses spontaneously. The most conspicuous question is why ROP in some premature infants progresses despite rigorous and timely intervention while in other cases with similar clinical characteristics it regresses. Evidence has suggested that African-American infants are less prone to severe outcome ROP than white infants and Alaskan natives develop threshold ROP earlier than non-natives. This racial variation suggests that genetic, socioeconomic, or dietary factors may be involved.[14] Poor early weight gain in postnatal period has been observed to be a risk factor for development of severe ROP.[15,16]

Table : Incidence and risk factors of retinopathy of prematurity

First author Year	Screening criteria	n	Incidence	Risk factors
Gopal L 1995[12]	Premature neonates with birth weight <2000 g	50	ROP: 38% (19/50) Threshold ROP: 16% (8/50)	No formal analysis. All with threshold ROP had received oxygen and 6 of 8 had received blood transfusion.
Charan R 1995[6]	Birth weight ≤1700 gm& admitted to the neonatal unit	165	ROP: 47% (78/165)	Not studied
Maheshwasri R 1996[8]	Gestation <35 wk or birth weight <1500 g or premature neonate needing oxygen for more than 24 h	66	ROP: 20% (13/66) Threshold ROP: 6/66 (9.1%)	Not studied
Rekha S 1996[11]	Gestation <35 wk or birth weight <1500 g	100	ROP: 46% (46/100) Threshold ROP: 9/100 (9%)	Anemia, duration of oxygen therapy
Varughese S 2001[13]	Gestation <34 wk or birth weight <1500g	79	ROP: 52% (41/79) Threshold ROP: 6.3% (5/79)	Not studied
Aggarwal R 2002[9]	Gestation <35 wk or birth weight <1500 g or premature neonate needing oxygen for more than 24 h	76	ROP: 32% (24/76) Threshold ROP: 2/76 (2.6%)	Apnea, clinical sepsis, male gender
Gupta VP 2004[7]	Gestation <35 wk or birth weight <1500 g	60	ROP: 21.7%	Apnea, sepsis, oxygen therapy
Dutta S 2004[10]	Gestation ≤32 wk or birth weight ≤1700 g or premature babies of any gestation who have received prolonged oxygen therapy (≥ 30 days)	108	Not reported	Administration of packed cells and double-volume exchange transfusion
Chaudhari S 2009[5]	Gestation ≤32 wk or birth weight < 1500 g or additional risk factors	552	ROP: 22.3% (123/552) Threshold ROP: 7.4% (41/552)	Apnea, septicemia and oxygen therapy
Sharma P 2009[17]	Preterm infants with birth weight ≤1500 g or gestation ≤32wk. Infants with birth weight 1501-1800 g or gestation 33-34 wk screened if additional risk factors present	704	ROP: 11.9% (84/704) 33 (4.7%) infants had severe ROP requiring laser therapy	Respiratory distress syndrome

Diagnosis

A screening program is needed for early diagnosis and secondary prevention of visual loss due to ROP in at-risk neonates. For documentation of the deterioration or regression of ROP, classification of degrees of severity for therapeutic interventions, and consistent reporting in clinical trials the International Classification of ROP (ICROP) is used.[18] ICROP describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent (clock hours).

Table : Classification of Retinopathy of Prematurity

1. Location	Zone I	Circle with optic nerve at centre and a radius of twice the distance from optic nerve to macula
	Zone II	From edge of Zone I to the nasal ora serrata nasally and equator temporally
	Zone III	Lateral most crescent shaped area from Zone II to ora-serrata temporally
2. Severity	Stage 1	Presence of thin white demarcation line separating the vascular from avascular retina
	Stage 2	The line becomes prominent because of lifting of retina to form a ridge having height and width
	Stage 3	Presence of extra retinal fibro-vascular proliferation with abnormal vessels and fibrous tissue arising from the ridge and extending into vitreous
	Stage 4	Partial retinal detachment; not involving macula (4A) or involving macula (4B)
	Stage 5	Complete retinal detachment
3. Plus disease		Presence of dilatation and tortuosity of posterior retinal vessels. Associated with vitreous haze, pupillary rigidity
4. Extent		Extent of involvement of the retina as expressed as clock hours (30 degree sectors)
5.Pre-plus disease		Vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal

Some **definitions** used in relation to ROP are as follows:-

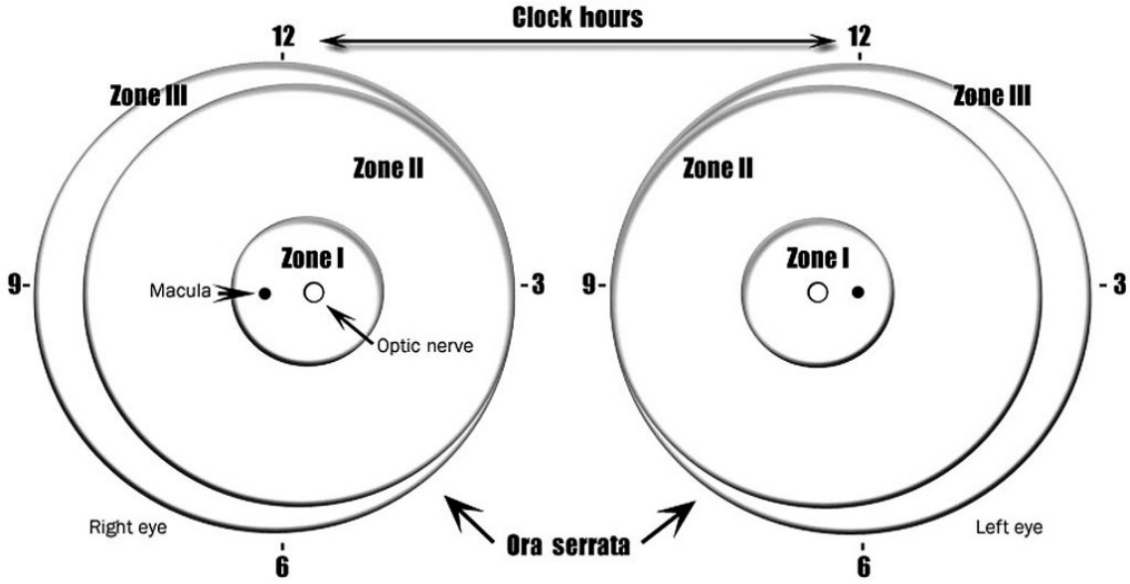
Aggressive posterior ROP (AP-ROP): A rapidly progressing, severe form of ROP. If untreated, it usually progresses to stage 5 ROP. The characteristic features of this type of ROP are its posterior

location, prominence of plus disease, and the ill-defined nature of the retinopathy. This may not have classical ridge or extraretinal fibrovascular proliferation. This rapidly progressing retinopathy has been referred previously as "type II ROP" and "Rush disease".Observed most commonly in Zone I, but may also occur in posterior Zone II.

Threshold disease: Presence of stage 3 with plus disease in Zone I or II, extending in 5 or more contiguous or 8 cumulative clock hours (30 degree sectors).

Pre-threshold disease: Presence of less than threshold disease in Zone 1, or stage 2 plus disease in Zone 2, or stage 3 (without plus) disease in Zone 2, or stage 3 plus disease with extent less than that for threshold disease.

Figure : International Classification of Retinopathy of Prematurity (ICROP) zones



Protocol for screening

The aim of the screening programme is to detect ROP early, follow it up closely during its evolution and treat if it reaches a potentially serious severity.

What is the 'screening window'

Progression of ROP follows a distinct time-table according to the post-menstrual age of the baby. Hardly any ROP is detected before 32 weeks of gestation. The median age for detection of stage 1 ROP is 34 weeks. Pre-threshold ROP appears at 36 weeks of post-menstrual age and threshold disease at 37 weeks. Vascularization is complete by 40 weeks of gestation. Thus the crucial period for detection of ROP is from 32 weeks to 40 weeks of post-menstrual period. The critical phase is from 34-35 weeks to 37-38 weeks age during which the progression of the disease takes place and treatment may have to be instituted. It may also be noted that ROP usually does not develop before 2 weeks of postnatal age.

Which babies should be screened?

Selecting neonates for screening depends on incidence of ROP at different gestation ages. Gestation and birth weight cut-off for screening shifts lower as smaller and sicker neonates start surviving. Based on current incidence and risk factors reported in Indian literature following group of neonates should be screened.

- Babies with birth weight <1500 g
- Babies born at ≤32 weeks of gestation
- Selected preterm infants with a birth weight between 1500 and 2000 g or gestational age of more than 32 weeks with sickness like need of cardiorespiratory support, prolonged oxygen therapy, apnea of prematurity, anemia needing blood transfusion and neonatal sepsisorbelieved by their attending pediatrician or neonatologist to be at high risk.This 'third criterion' is important as it brings in many more larger babies into the screening guidelines without raising the screening parameters.[19]

When and how often to screen

First screening examination should be carried out at 31 weeks of gestation or 4 weeks of age, whichever is later (Table 3).[20] A good rule to remember is first screening at 1 month of postnatal age in babies born at >26 weeks of gestation age.

Table : Timing of First Screening Eye Examination Based on Gestational Age at Birth[20]

Gestation age at birth (weeks)	Age at initial examination	
	Postmenstrual age	Chronological age
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings.

- 1-week or less follow-up
    - Stage 1 or 2 ROP: Zone I
    - Stage 3 ROP: Zone II
- 1- to 2-week follow-up
    - Immature vascularization: Zone I—no ROP
    - Stage 2 ROP: Zone II
    - Regressing ROP: Zone I

- 2-week follow-up
    - Stage 1 ROP: Zone II
    - Regressing ROP: Zone II
- 2- to 3-week follow-up
    - Immature vascularization: Zone II—no ROP
    - Stage 1 or 2 ROP: Zone III
    - Regressing ROP: Zone III

Findings that suggest further examinations are not needed include:

- Zone III retinal vascularization attained without previous Zone I or II ROP
- Full retinal vascularization
- 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

Where to examine the baby?

Neonates are best examined in the neonatal unit itself under supervision of attending pediatrician. It is not wise to transport small babies to ophthalmic outpatient or ward for examination.

How to dilate the pupils?

Pupils are dilated with Phenylephrine 2.5% and Tropicamide 0.5%. One drop of Tropicamide is instilled every 10-15 minutes for 4 times starting 1 hour before the scheduled time for examination. This is followed by phenylephrine, one drop just before examination. Phenylephrine is available in 10% concentration; it should be diluted 4 times before use in neonates. Repeated instillation of phenylephrine is avoided for the fear of hypertension.

What does the examination entail?

Screening of ROP involves indirect ophthalmoscopy using 20 D or 28/30 D lens by an experienced ophthalmologist. After instilling a topical anesthetic drop like Proparacaine, a wire speculum is inserted to keep the eye-lids apart.First the anterior segment of the eye is examined to look for tunica vasculosa lentis, pupillary dilation, and lens / media clarity; followed by the posterior pole to look for plus disease; followed by sequential examination of all clock hours of the peripheral retina. A scleral depressor is often used to indent the eye externally to examine areas of interest, rotate and stabilize the eye.

How to record findings during screening?

Ophthalmological notes should be made after each ROP examination, detailing zone, stage and extent in terms 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 with the baby's medical record.

Figure : Retinopathy of Prematurity Screening Examination Record Sheet

What precautions are taken during examination?

ROP screening examinations can have short-term effects on blood pressure, heart rate and respiratory function in the premature baby.[21] The examinations should be kept as short as possible and precautions taken to ensure that emergency situations can be dealt with promptly and effectively.

Eye examination during screening lasts several minutes and may cause considerable pain to the neonate. A systematic review and meta-analysis comprising four studies has reported that oral sucrose reduces pain during eye examination.[21] Of two studies reporting the role of topical proparacaine drops one has observed significant pain reduction.

Discomfort to the baby should be minimized by administering oral sucrose just before examination, pretreatment of the eyes with a topical proparacaine and swaddling the baby. Baby should not have been fed just before examination to avoid vomiting and aspiration. Hand washing should be done and asepsis maintained.

Use of wide-field digital camera (RetCam) for screening

A wide-field digital camera (RetCam) capable of retinal imaging in preterm infants has been evaluated as an alternative to indirect ophthalmoscopy for screening. Retinal images taken by camera can be stored, transmitted to expert, reviewed, analyzed and sequentially compared over time and are useful for telemedicine purposes Studies comparing RetCam with the indirect ophthalmoscope have reported variable sensitivity and good specificity.[22] However, due to high cost and due to limitations in diagnostic sensitivity, specificity, and accuracy when image quality is poor it is not recommended to replace bedside ophthalmoscopic examination.Digital fundus images can be used as a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy.

Treatment

What is the indication?

Early Treatment of Retinopathy of Prematurity (ETROP) trial recruited neonates at 26 centres in the US and compared early treatment of high-risk prethreshold with conventional thresholdtreatment.[23]401 babies meeting the criteria for 'high-risk' of an unfavourable outcomewith prethreshold in at least one eye were randomized to receive either early or conventionaltreatment. The level of risk was determined by a risk analysis programme which used, among other factors, degree of ROP (stage, zone and presence of plus), rate of ROPprogression, birthweight, gestational age and ethnicity to classify eyes as at either 'high-risk' (i.e.≥15% chance) or 'low-risk' (<15% chance) of an unfavourable outcome without treatment.The results showedan overall significant benefit for the early treatment of eyes with high-risk prethreshold disease. Based on results of ETROPtwo new terminologies have been suggested:

Type 1 ROP:

- Zone I, any stage ROP with plus disease
- Zone I, stage 3 ROP with or without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

Type 2 ROP:

- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease

Peripheral retinal ablation should be carried out for all cases with type 1 ROP and continued serial examinations are advised for type 2 ROP.

What are treatment modalities available and what are their advantages & disadvantages?

Peripheral retinal ablation of avascular retina anterior to the ridge can be done by either cryotherapy or diode laser. Diode laser ablation has replaced cryotherapy due to lower rate of postoperative ocular and systemic complications and less damageto the adjacent tissues compared with cryotherapy. Other advantages are that the laser spotsare visible during treatment minimizing the risk of missing areas requiring treatment, and thatlaser equipment is portable allowing use outside of the operating theatre.The procedure can be carried out under general anesthesia or under sedation depending on the feasibility and expertise. Treatment forROP should include the entire avascular retina anterior to the ridge with burn spacing of between0.5 to 1 burn-widths apart.

Pre-anesthetic medication

Oral feeds should be discontinued 3 hours prior to the procedure. Baby should be started on intravenous fluids, and put on cardio-respiratory monitor. Dilatation of pupil is done by using 0.5% Tropicamide and 2.5% phenylephrine as described in the section on protocol for screening.

Anesthesia/ Sedation

Topical anaesthesia alone provides insufficient analgesia for ROPtreatment and should not be used.Babies may be treated under adequate sedation and analgesia in an operation theatre if this canbe arranged in a timely way. If shifting to operation theatre is not possible or is causing delay in treatment, babies may be treated more rapidly in the neonatal unit under adequate sedation and analgesia..

Procedure

Both the eyes can be treated at the same sitting time unless contraindicated by instability of the baby. If baby is not tolerating the procedure, consider abandoning the procedure for the time being. Vital signs and oxygen saturation should be monitored very closely.

Table : Preparation for laser ablative therapy

❖ Take consent ❖ Ensure good pupillary dilatation ❖ Nil by mouth 3 h prior to procedure

- Start on intravenous fluids
- Put on vital sign monitor/pulse oximeter
- Warmer for maintaining temperature
- Arrange equipment and check functioning thereof
  - Intubation equipment
  - Endotracheal tubes No. 2.5, 3, 3.5
  - Resuscitation bag & face masks
  - Oxygen delivery system
  - Syringes
  - Infusion pumps
  - Ventilator
- Arrange drugs, fill syringes in advance with drugs in appropriate dilution and label them : morphine, midazolam, normal saline 10% dextrose, adrenaline

Monitoring after laser therapy

After laser therapy first examination should take place 5-7 days aftertreatment and should be continued at least weekly for signs of decreasingactivity and regression. Re-treatment should be performed usually 10-14 days after initialtreatment when there has been a failure of the ROP to regress.

Post-operative care

- The baby should be closely monitored. If condition permits, oral feeds can be started shortly after the procedure.
- Premature babies, especially those with chronic lung disease may have increase or re-appearance of apneic episodes or an increase in oxygen requirement. Therefore they should be carefully monitored for 48-72 hours after the procedure.
- Antibiotic drops (such as chloramphenicol) should be instilled 6-8 hourly for 2-3 days.

Prevention

Judicious oxygen therapy

Oxygen is a drug and it should be administered in a quantity that is absolutely necessary. Each neonatal care unit should have a written policy outlining appropriate use of oxygen therapy. If a preterm neonate born at < 32 weeks gestation needs resuscitation at birth, inhaled oxygen concentration (FiO_2) should be titrated to prevent hyperoxia and achieve gradual increase in oxygen saturation (70% at 3 minute and 80% at 5 minute after birth).[24] During acute care of a sick preterm neonate, ROP is more likely to develop if partial pressure of oxygen in arterial blood is more than 80 mm Hg.[25] Oxygen level in blood should be continuously monitored using pulse oximeter. It has been observed that if oxygen saturation in a baby on oxygen therapy is kept between 85% and 93%, in about 90% samples partial pressure of oxygen is in desirable range (40 to 80 mm Hg).[26] Various observational studies have reported that incidence and severity of ROP is lowered if oxygen saturation targets are kept in desirable range and if units implement written policies regarding oxygen administration and monitoring.[27,28]During recovery phase of respiratory illness in preterm neonates, targeting higher oxygen saturations has been associated with increased incidence/severity of bronchopulmonary dysplasia without any benefit in stopping progression of ROP or improving growth and development.[29,30]

Judicious use of blood transfusions

Transfusion of packed RBCs is another risk factor of ROP. Adult RBCs are rich in 2,3 DPG and adult Hb binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue. Packed cell transfusions should be given when hematocrit falls below following ranges: ventilated babies 40%, babies with cardio-pulmonary disease but not on ventilators 35%, sick neonates but not having cardiopulmonary manifestations 30%, symptomatic anemia 25% and asymptomatic anemia 20%.

Vitamin E Supplementation

Very low birth weight neonates should receive 15-25 IU of vitamin E daily as supplement. However, higher doses given by intravenous route have been associated with increased risk of neonatal sepsis.[31]

Prenatal steroids

Use of prenatal steroids is a well-known approach to prevent respiratory distress and intraventricular hemorrhage, two important risk factors of ROP. Although there are some concerns that prenatal steroids may induce ROP, this is not borne out by other studies. We believe prenatal steroids prevent

acute illnesses in premature babies and should be administered to all mothers with preterm labor between 24-34 weeks of gestation. The preferred preparation of steroids for prenatal used is betamethasone in two doses of 12 mg each given intramuscularly, 24 hours apart.

Bevacizumab

Intravitreal injection of bevacizumab, a neutralizing anti-VEGF moleculehas been demonstrated to diminish the neovascularresponse significantly in animal models.[32] However, due to uncertainties with respect to the dosing, frequency, timing, and adjunct therapiesto be used and potential to cause serious systemic adverse effects, use of bevacizumab is not recommended outside the scope of clinical trial.

Quality improvement

Roles and responsibilities

- All units caring for babies at risk of ROP should have a written protocol in relation to the screening for, and treatment of, ROP. This should include responsibilities for follow-up of babies transferred or discharged from the unit before screening is complete.
- If babies are transferred either before ROP screening is initiated or when it has been started but not completed, it is the responsibility of the consultant neonatologist to ensure that the neonatal team in the receiving unit is aware of the need to start or continue ROP screening.
- Whenever possible ROP screening should be completed prior to discharge. There should be a record of all babies who require review and the arrangements for their follow-up.
- For babies discharged home before screening is complete, the first followup out-patient appointment must be made before hospital discharge and the importance of attendance explained to the parents.

Auditing

Following outcomes should be regularly audited in units with ROP screening and treatment programme.

- Completeness of screening programme: Percentage of babies <32 weeks GA or<1501g birthweight who receive at least one ROP eye examination
- Timing of first screen:Percentage of babies < 27 weeks GAreceiving a first ROP screeningexam by 4 weeks of postnatal age.
- ROP Treatment: Percentage of babies with any zone 1 ROPwho receive treatment
- Timing of treatment: Percentage of babies needing ROP treatment for their ROP who are treated within 48 hours of the decision totreat being made

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