Retinopathy of Prematurity

Abstract

With improving survival of very low birth infants in India, Retinopathy of Prematurity (ROP) is emerging as a significant problem. The most important risk factor in the pathogenesis of ROP is prematurity. Other factors like frequent blood transfusions; sepsis, apnea and problems with oxygenation have also been implicated in the causation of ROP. Essentially asymptomatic in the initial stages, a good screening program is essential for the early detection and treatment of this condition. Description of the various stages of ROP has been included in the protocol. Guidelines regarding 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 program.
Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina among premature babies. Its incidence increases with decreasing gestation and birth weight. As many as 27 to 35 percent infants less than 1500 g birth weight and 16 to 48 percent infants less than 1000 g birth weight develop some degree of ROP. Apart from prematurity, the other risk factors of ROP include: hyperoxia, hypoxia, hypotension, acidosis, blood transfusions, sepsis, antioxidant deficiency, patent ductus arteriosus and apnea. ROP can occur in babies who have not received oxygen.

**CLASSIFICATION OF ROP**

*Classification of ROP is shown in Table 1.*

<table>
<thead>
<tr>
<th>Table 1. Classification of ROP[^5-7]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Location</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2. Severity</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3. Plus disease</td>
</tr>
<tr>
<td>4. Extent</td>
</tr>
<tr>
<td>5. Pre-plus disease</td>
</tr>
</tbody>
</table>

[^5-7]: Accessed from www.newbornwhocc.org
Some **definitions** used in relation to ROP are as follows:-

**Aggressive posterior 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 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.

**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 weeks to 37 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?*

Indications: Any one of the following:
• 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 an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk

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 2). A good rule to remember is first screening at 1 month of postnatal age in babies born at >26 weeks of gestation age.

Table 2: Timing of First Screening Eye Examination Based on Gestational Age at Birth

<table>
<thead>
<tr>
<th>Gestation age at birth (weeks)</th>
<th>Age at initial examination</th>
<th>Postmenstrual age</th>
<th>Chronological age</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>31</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>31</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>31</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>31</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>31</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>31</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>32</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>33</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>34</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>35</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>36</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

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

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

• 2-week follow-up
  o Stage 1 ROP: Zone II
  o Regressing ROP: Zone II

• 2- to 3-week follow-up
  o Immature vascularization: Zone II—no ROP
  o Stage 1 or 2 ROP: Zone III
  o 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 1.0%. One drop of Tropicamide is instilled every 10-15 minutes for 4 times starting instilled together at 10 minutes interval for a
period of 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.

*What does the examination entail?*

Screening of ROP involves indirect ophthalmoscopy using 20 D or 30 D lens. A wire speculum is used to keep the eye-lids apart.

*What precautions are taken during examination?*

Baby should not have been fed just before examination to avoid vomiting and aspiration. Hand washing should be done and asepsis maintained. Discomfort to the baby should be minimized by pretreatment of the eyes with a topical anesthetic agent such as proparacaine; consideration also may be given to the use of oral sucrose.
ABLATION THERAPY OF ROP

What is the indication?

Based on results of Early Treatment for Retinopathy of Prematurity Randomized Trial\textsuperscript{8} two new terminologies have been suggested:

Type 1 ROP\textsuperscript{8}:

- 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\textsuperscript{8}:

- 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 can be done by either cryotherapy or diode laser. The advantages and disadvantages of these procedures are shown in Table 3. Overall, laser is the preferred choice.
Table 3. Comparison of cryotherapy and laser ablation

<table>
<thead>
<tr>
<th>Cryotherapy</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trans-scleral ablation</td>
<td>• Direct ablation</td>
</tr>
<tr>
<td>• Very painful</td>
<td>• Less painful</td>
</tr>
<tr>
<td>• Needs baby to be put an ventilator during procedure</td>
<td>• No need to put the baby on ventilation</td>
</tr>
<tr>
<td>• Substantial lid swelling and conjunctival edema</td>
<td>• Less local complications</td>
</tr>
<tr>
<td>• Posterior retina difficult to reach</td>
<td>• Posterior retina can be reached more readily</td>
</tr>
<tr>
<td>• Myopia and retinal detachment machine are a problem</td>
<td>• Both these complications are less common.</td>
</tr>
</tbody>
</table>

**Cryotherapy**

Cryotherapy involves the insertion of a probe cooled with liquid nitrogen on the outer aspect of eye. The avascular retina is ablated by confluent spots of cryotherapy. This results in decreased release of the angiogenic factor, which is believed to induce retinal proliferation. Cryotherapy is a major procedure and is undertaken with the neonatal and ophthalmology teams in full readiness and after proper planning.

**Laser photo-coagulation**

It is a more recent technique and has replaced cryotherapy. Both Argon and Infrared diode lasers have been successfully used to ablate the avascular retina in a similar manner to that used in cryotherapy. The procedure can be carried out under general anesthesia or under sedation depending on the feasibility and expertise. Skilled ophthalmologist can successfully undertake laser ablation by simply immobilizing the child in wrapped sheets. We use laser therapy avoiding any kind of sedation.
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 1% Tropicamide and 2.5% phenylephrine as described in the section on protocol for screening.

Anesthesia/ Sedation

The procedure can be carried out under sedation supplemented by local anesthesia with topical anesthetic drops.

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 3: 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: midazolam, normal saline 10% dextrose, adrenaline
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 reappearance 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 OF ROP

ROP is, to a significant extent, a preventable disease. Following strategies help in reducing the incidence and severity of the disease:

Judicious oxygen therapy

Oxygen is a drug and it should be administered in a quantity that is absolutely necessary. Both hypoxia and hyperoxia are detrimental to the baby.\(^9\)\(^-\)\(^10\) Pulse oximetry is a practical way to regulate oxygen administration. Baby’s oxygen saturation should be maintained between 90-93%. Alarm limits should be set at 88% and 95%. Arterial blood gases should be checked periodically. \(\text{PaO}_2\) should be maintained between 50 and 70 mm Hg. If oxygen is being administered by oxygen hood, its concentration (\(\text{FiO}_2\)) should be monitored using oxygen analyzer. This will ensure that the administered oxygen remains in the desired concentration.

Permissive hypercapnia

Hypocapnia is a risk factor of ROP. In infants on ventilators, \(\text{PaCO}_2\) can be allowed to be in the range of 50-60 mm Hg provided the pH is above 7.25. This permissive hypercapnia will enable lower ventilatory settings minimizing tendency for chronic lung disease which necessitates prolonged oxygen use.
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 which 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%.

Strict clinical and electronic monitoring

Low and high blood pressure as well as hypoxia and hyperoxia are risk factors of ROP. Close clinical and electronic monitoring helps in detection of these disorders early, making prompt treatment possible.

Vitamin E Supplementation

All babies with birth weight less than 1500g should receive 15-25 IU of vitamin E daily as supplement. Vitamin E deficiency predisposes to ROP.

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.

ROP surveillance and management programme prevents the disease
We believe that when a neonatal unit runs an effective ROP surveillance and management programme, the incidence and severity of this disease decreases. This happens because the physicians and nurses become sensitized to the practices that lead to ROP and they make conscious efforts to minimize them.
REFERENCES


