Retinopathy of Prematurity: An Update

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Introduction
Retinopathy of prematurity (ROP) was originally designated as retrolental fibroplasias by Terry in 1952 who related it with premature birth.1 Term ROP was coined by Heath in 1951.2 It is a disorder of development of retinal blood vessels in premature babies. Normal retinal vascularization happens centrifugally from optic disc to ora. Vascularization up to nasal ora is completed by 8 months (36 weeks) and temporal ora by 10 months (39–41 weeks).3

The incidence of ROP is increasing in India because of improved neonatal survival rate. Out of 26 million annual live births in India, approximately 2 million are <2000 g in weight and are at risk of developing ROP.3 In India the incidence of ROP is between 38 and 51.9% in low-birth-weight infants.3,4

Screening guidelines

American Academy of Pediatrics guidelines5

- Infants with birth weight of ≤1500 g.
- Gestational age of 30 weeks or less.
- Infants with birth weight between 1500 and 2000 g or gestational age of >30 weeks with unstable clinical course.

Indian scenario6

- Birth weight <1700 g
- Gestational age at birth <34–35 weeks
- Exposed to oxygen >30 days
- Infants born at <28 weeks and weighing <1200 g are particularly at high risk of developing severe form of ROP
- Presence of other factors such as respiratory distress syndrome, sepsis, multiple blood transfusions, multiple births (twins/triplets), apneic episodes, intraventricular hemorrhage increase risk of ROP. In these cases screening should be considered even for babies>37 weeks gestation or >1700 g birth weight.

The first screening should be done within 4 weeks (30 days) of life in infants with age >28 weeks of gestational age. Screening should be done earlier (2–3 weeks after birth) if gestational age is <28 weeks or birth weight is <1200 g.4 Screening should be done by an ophthalmologist who is well versed with indirect ophthalmoscopy in ROP babies. Child should be fed 1 hour prior to examination. We use 1 ml of 10% phenylephrine (Drosyn) mixed in 3 ml of 1% tropicamide (after discarding 2 ml from 5 ml bottle) for pupillary dilatation. These combination drops are used every 15 minutes for 3 times. Punctum occlusion is mandatory after instilling the drops to reduce the systemic side effects of medication. Excess eye drops should also be wiped off to prevent absorption through cheek skin. If the pupil does not dilate in spite of proper use of medication, presence of plus disease should be suspected. Repeated installation of topical drops should be avoided to prevent systemic problems. Sterile Alfonso speculum is used to retract the lids and wire vects for gentle depression.

High-quality retinal images obtained using commercially available wide-angle fundus camera like the Retcam followed by Telescreening by a trained ophthalmologist can also be done. In developing countries like India where majority of people live in remote areas which may not have access to the tertiary-level care, telescreening may bring more children into the screening program. This model has been successfully used by Vinekar et al. in Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KIDROP).7 The follow up schedule for these babies is given in Table 1.

Role of laser

Since the stimulus for abnormal vessels comes from the avascular retina therefore ablating the peripheral avascular retina is believed to cause regression of the ROP. Earlier the CRYO-ROP Study7 treatment guidelines were followed; with the results of Early treatment for retinopathy of prematurity (ETROP study)8 there has been a paradigm shift in treatment to laser therapy from CRYO therapy. Laser therapy significantly allows more precision of treatment as well as reduces the unfavorable side effects of the cryotherapy and has more than 90% successful results.8 Laser treatment protocol according to ETROP is given in Table 2.

Treatment guidelines

Laser is done using indirect laser ophthalmoscope under topical anesthesia after pupillary dilatation under care of an anesthetist in the operation theatre. The entire avascular retina up to the ora serrata should be ablated with near confluent burns (0.5–1 burn width apart) up to the ridge. Heart rate and apnea spells should be monitored throughout the laser.9 In severe forms of disease not responding to this laser photoagulation further laser to the ridge as well as posterior to
ridge has also been shown to be effective in severe cases of ROP. This has caused regression of the disease in some cases and avoided the progression of tractional retinal detachment.

Follow-up visits after laser treatment are usually weekly till the ROP regresses and involution of all tractional elements is seen and vascularization reaches the temporal ora.

Table 1  Follow-up schedule for ROP babies

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Immature vascularization, no ROP</th>
<th>ROP Stage 1 or 2</th>
<th>ROP Stage 3</th>
<th>Regressing ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week or less</td>
<td>Zone I or immature retina extends into posterior zone II</td>
<td>Stage 1 or 2, zone I</td>
<td>Zone III, zone II pre-threshold</td>
<td>Unequivocally regressing ROP, Zone I</td>
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<tr>
<td>1–2 weeks</td>
<td>Posterior zone II</td>
<td>Stage 2, zone II</td>
<td></td>
<td>Unequivocally regressing ROP, Zone II</td>
</tr>
<tr>
<td>2 weeks</td>
<td>Zone II</td>
<td>Stage 1, zone II</td>
<td></td>
<td>Regressing ROP, Zone III</td>
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<tr>
<td>2–3 weeks</td>
<td></td>
<td>Stage 1 or 2, zone III</td>
<td></td>
<td></td>
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</tbody>
</table>

Fig. 1  (A) Stage 1: Demarcation line. (B) Stage 2: Ridge. (C) Stage 3: Ridge with extra retinal fibrovascular proliferation. (D) Stage 4A: extrafoveal retinal detachment. (E) Stage 4B: fovea involving retinal detachment. (F) Plus disease with dilated and tortuous retinal vessels
Role of anti-vascular endothelial growth factor (VEGF)

In recent times, anti-VEGF has also been used in severe forms of ROP, especially those not responding to laser photocoagulation. Its role, however, is very controversial. VEGF is needed in premature babies for the normal organogenesis and vasculogenesis. Also systemic absorption may cause vascular development delay in other organs in these premature babies. Therefore, it is not recommended by many as the first-line therapy.1

BEAT ROP study which compared bevacizumab monotherapy with conventional laser therapy showed promising results for stage 3+ ROP in zone 1 but not in zone 2.11 In this study, peripheral retinal vessels continued in normal fashion after treatment with intravitreal bevacizumab. This study was too small to assess the safety profile in these babies.11

The follow-up period after mono therapy is unpredictable as there can be a recurrence of neovascularization even beyond 54 weeks of post-gestational age. It is recommended that follow-up should be continued till there is no evidence of tractional elements and the vascularization reaches ora.5 In Zone 1 ROP, the Laser treatment outcomes are poorer. Treatment with anti-VEGF followed by a 4–5 days later with laser treatment in these cases has improved the efficacy of laser along with a reduced need for extensive laser especially at the posterior pole.12 In a study by Chen et al. both bevacizumab and ranibizumab had similar efficacy at the end of 1 year in terms of ROP regression and visual acuity.13

On the basis of available literature indication for anti-VEGF therapy can be enumerated as:

1 Primary therapy for aggressive posterior zone 1 disease (APROP).

2 Aggressive anterior ROP or media haze due to aggressive posterior disease to improve visualization for laser treatment.

3 Failed laser treatment leading to persistent neovascularization, tractional elements or tractional retinal detachment prior to surgery.

Role of surgery

Surgery is done for tractional retinal detachment (TRD) repair as seen in Stages 4 and 5 ROP. The aim for surgical intervention in Stage 4 ROP is to prevent progression of retinal detachment. Scleral buckling (placing 240 band at the height of the TRD by making sclera tunnels in all quadrants) is done for Stage 4A ROP with only peripheral tractional retinal detachment. This surgery does not involve the removal of membranes formed on the retina but by causing peripheral scleral indentation reduces the effective TRD. This procedure can be combined with cryotherapy or laser to any peripheral persistent new vessels. The encircling band needs to be removed once the child is 1 year of age to allow normal growth of the eyeball and to reduce the amount of anisometropia induced by the buckle.

Lens sparing vitrectomy (LSV) has shown promising results in Stages 4A and 4B. Long-term results with lens sparing vitrectomy were favorable in the study by Trese et al.: 82.1% (Stage 4A), 69.5% (Stage 4B) and 42.6% (Stage 5) showing successful anatomical reattachment of retina with lens being clear for at least the first decade of life.14 Bhende et al. also reported 82% anatomical success in 4A stage ROP and 50% in Stage 4B ROP after single procedure.15 25-Gauge vitrectomy is now commonly used for ROP surgery. Finer instrumentation and more effective microvit systems in small gauges are useful during membrane dissection. However, modification of the technique in the form of conjunctival dissection as well as suturing of the sclerotomies at the end of surgery may be necessary.16 Modern vitreo-retinal surgical tools like the infusion light pipe, binocular indirect ophthalmoscopy (BIOM) which allows wide-angle viewing has reduced the risk of creating iatrogenic retinal breaks and also sparing of lens, allowing easy visual rehabilitation in these children.17

In Stage 5 ROP, the results of surgical intervention are poor. It usually involves the removal of the lens. Gopal et al. had anatomical success with the attachment of posterior pole in 22.5% of cases with lens sacrificing vitrectomy though visual results were unsatisfactory with only two children showing mobile vision out of 96 eyes.18 Closed globe vitrectinal surgery was done in all these eyes with Stage 5 ROP. The aim of the surgery for Stage 5 ROP is to clear all preretinal tissue up to the disc and open the peripheral trough all round. In most instances, bimanual surgery under viscoelastic is performed. Anterior chamber (AC) maintainer to keep the IOP under control during surgery is also used. Fixation of infusion cannula

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### Table 2

Laser treatment protocol for ROP according to ETROP 8

<table>
<thead>
<tr>
<th>Zone 1</th>
<th>No Plus</th>
<th>Stage 1</th>
<th>Follow</th>
<th>Stage 2</th>
<th>Follow</th>
<th>Stage 3</th>
<th>Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus</td>
<td></td>
<td>Stage 1</td>
<td>Treat</td>
<td>Stage 2</td>
<td>Treat</td>
<td>Stage 3</td>
<td>Treat</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Zone 2</th>
<th>No Plus</th>
<th>Stage 1</th>
<th>Follow</th>
<th>Stage 2</th>
<th>Follow</th>
<th>Stage 3</th>
<th>Follow</th>
</tr>
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<tbody>
<tr>
<td>Plus</td>
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<td>Stage 2</td>
<td>Follow</td>
<td>Stage 3</td>
<td>Treat</td>
</tr>
</tbody>
</table>
through pars plicata is impossible in these cases because the retina is pulled up to the lens.

Open sky vitrectomy (through a trephined corneal opening) has also been advocated by some especially in cases with corneal opacity.19 It has the advantage of allowing two hand dissection from a large anterior incision but maintenance of intraocular pressure is difficult.

**Conclusion**

Considering the poor outcome of surgery in end-stage ROP timely intervention in the form of laser treatment is the best treatment option. There is need to increase the awareness of the disease to make sure these babies can be treated on time. Also there is a need of more numbers of specialized vitreoretinal surgeons who can handle these babies.

**References**