Management of retinopathy of prematurity

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Summary  Retinopathy of prematurity (ROP) has been recognised as an important cause of childhood blindness. It is now a treatable disease with a reduced incidence of resulting blindness. The incidence of ROP in older premature babies has declined and a new pattern of ROP has emerged attributed to increased survival of very low birth weight infants. This may require a different management approach with treatment at an earlier stage. Here we give an overview of the natural history of ROP, terminology, screening and diagnosis. We also describe the examination and treatment of the infant with ROP. While significant reductions in the disease have occurred, further research is required to fully understand and prevent the disease.

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KEYWORDS
Retinopathy of prematurity; Threshold disease; Plus disease; Cryotherapy; Laser

Practice points
• ROP still occurs but can be significantly reduced by active treatment
• The most important risk factors for ROP are gestational age and the birth weight
• Once stage 3 disease develops there is a significant risk of poor structural or visual outcome
• The focus of screening is to identify disease requiring treatment within the window of treatment opportunity

• Retinal laser has superseded cryotherapy, however both are effective treatments
• The parents must be informed about the nature of the disorder, the risk of blindness and the expected success rate
• Vitreoretinal surgical management is not recommended in advanced disease

Introduction

Babies most at risk of developing severe retinopathy of prematurity (ROP) requiring treatment comprise the most immature section of the preterm population. Advances in neonatal intensive care, including the meticulous administration and
monitoring of oxygen have largely eliminated the risk of severe ROP for the more mature preterm babies, so that nowadays severe ROP is mostly confined to babies with a birth weight (BW) under 1000 g and a gestational age (GA) of 31 weeks or less and blinding disease is rarely seen in larger babies. In the United Kingdom, mild ROP is common and severe disease requiring treatment affects around 1.8% of the preterm population screened.

The International Classification of Retinopathy of Prematurity (ICROP) 1984 and 1987 provided a simple description of this condition, while the Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP) demonstrated that treatment could significantly reduce blindness. Thus the CRYO-ROP Study generated the need for babies at risk to be examined and the ICROP provided the tools that made screening possible. In the UK, the first guidelines for ROP screening were published in 1990. Since that time, much has changed, such as: the possibility of medical management, the indications for surgical intervention and treatment methods, and finally the classification is being revised.

### Natural history of ROP

Initially, the retina is avascular and vascularisation proceeds centrifugally from the optic disc from about 16 weeks’ GA, so that the avascular areas of the retina gradually contract, this process being complete by about term. Both vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) are implicated in normal vascular development and ROP pathogenesis. A better understanding of the vascular development is an area of current investigation.

Risk factors of ROP include measures of immaturity (low BW and low GA), metabolic acidosis and sepsis. Systemic steroids administered to the mother prior to preterm delivery have been shown to reduce the risk of ROP. Surfactants do not significantly alter the proportion of babies at risk who develop severe ROP and the role of systemic vitamin E is controversial. Clinical trials of reduced light exposure in the nursery have shown that this intervention has no impact on the incidence of ROP. The role of genetic factors remains unclear. Norrie disease gene mutations have been found in

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tr>
<td>Stage</td>
<td>1 Demarcation line at the advancing edge of the retinal blood vessels (Fig. 1)</td>
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<tr>
<td></td>
<td>2 Ridge</td>
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<td></td>
<td>3 Ridge with Extraretinal Fibrovascular Proliferation (Fig. 2)</td>
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<tr>
<td></td>
<td>4 Retinal detachment—partial retinal detachment</td>
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<td></td>
<td>5 Total Funnel Retinal detachment</td>
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<tr>
<td>Location</td>
<td>Zone I–III This predictable pattern of retinal vascularisation was formally recognised by the International Classification of Retinopathy of Prematurity (ICROP) in 1984 and 1987, which divided the retina into progressive concentric zones. The location of ROP is described in terms of these three arbitrarily defined ICROP zones which are centred around the optic disc (Fig. 3).</td>
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<tr>
<td>Extent</td>
<td>1–12 'Plus' disease This is described by clock hours by 30 degree sectors</td>
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<tr>
<td></td>
<td>'Plus' disease is characterised by active progression and at a more advanced stage the iris becomes congested resulting in poor pupil dilatation. The presence of plus disease is an urgent indication for treatment (Fig. 4).</td>
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some infants with ROP, but the significance of this is still to be determined and ethnic factors may have some implications in ROP development. While the risk factors determine whether a baby will develop ROP, the time at which it develops and its subsequent rate of progression are both related mostly to postmenstrual age (PMA).

**Medical management of ROP**

Of all ROP risk factors, other than low GA and low BW, oxygen remains at the forefront and undoubtedly has a role to play in the aetiology of ROP. Keeping babies in low levels of oxygen reduced ROP requiring treatment. While these findings have stimulated considerable interest they have yet to make a general impact on neonatal care. It was hoped that the administration of supplemental oxygen might reduce ROP requiring treatment (presumably through a mechanism involving VEGF), unfortunately this proved not to be so. As Tin & Wariyar have pointed out, even after 50 years of debate there are many aspects that elude our understanding of what constitutes a safe level of oxygen at each stage of early postnatal life. The finding of associations between the duration of oxygen therapy and the development of ROP may simply indicate that the more systemically ill infants develop ROP.

**Terminology of ROP**

ROP is described by four parameters (Table 1)—severity by stage (Figs. 1 and 2), location (Fig. 3), extent and 'plus' disease (Fig. 4).

**Screening and diagnosis**

Since the demonstration, in 1988, by the CRYO-ROP trial that severe ROP can be successfully treated, the ophthalmologist has had a duty to screen for this condition. The focus of screening is to identify ROP that requires treatment and within the window of opportunity requiring treatment.

The current criteria for screening in the UK is babies born with a BW of <1500 g or a GA<32 weeks.

It is recommended that screening should commence between 6 and 7 weeks postnatal age (UK) and then at least every 1–2 weeks depending on severity of disease, until the retinal vessels have reached zone III or there is regression of disease.

There is a high failure rate of attending follow-up out-patient appointments for ROP screening, so the process should be completed, if possible, while the baby is in hospital.

**Examination**

**Examination technique**

1. Pupil dilatation by cyclopentolate 0.5% and phenylephrine 2.5% eye drops instilled at least 30 min prior to examination.
2. Indirect ophthalmoscope is the gold standard for ROP screening. The recent development of contact wide-field digital retinal imaging (e.g. RetCam 120) has opened up new opportunities for ROP service and research and is being increasingly used for routine screening. Since the image obtained at the cot side is projected onto a monitor it can be seen by parents and staff, thereby facilitating discussions and teaching about the condition and removing the need for multiple examinations. This technique may also be used for telemedicine.\textsuperscript{12}

**Record keeping**

ROP findings should be recorded both in the clinical records and also in a separate book for audit purposes.

**Information for parents**

Providing sensitive, balanced information is an essential component of this process to enable parents to be involved in decision-making. Written information should be available to inform them about the condition, the purpose of screening and treatment outcomes.

As soon as it is apparent that an infant has ROP that is close to and likely to advance to stage 3, it is preferable that the ophthalmologist personally, with a member of the Neonatal intensive Care Unit (NICU) staff present, discusses the issues with the parents.

**Treatment of acute ROP**

The CRYO-ROP study confirmed the success of cryotherapy treatment versus non-treatment. Over the past decade, cryotherapy has very largely been succeeded by argon laser treatment. Laser is now the preferred mode since the most severe forms of disease are more easily treated with laser than with cryotherapy. Although more time-consuming, it is less traumatic to the baby. However there remain a few specific indications for cryotherapy.
Rationale for treatment

The stimulus for abnormal vessel growth comes from the peripheral non-vascularised hypoxic retina. The fundamental principle of treatment is to remove, by cryotherapy or laser, the stimulus for vessel growth by ablating the peripheral avascular retina.

Criteria for treatment

The indication for treatment as reported in the CRYO-ROP study is ‘threshold’ ROP. The term ‘threshold’ denotes the ROP stage at which spontaneous and complete resolution is unlikely and the risk of blindness is predicted to be close to 50%.13 However, although the CRYO-ROP study improved outcome in 44.4% of eyes with a history of severe ROP, this is far from ideal and the need for more effective approaches to treatment is required. Further studies, such as that published recently by the Early Treatment for Retinopathy of Prematurity Cooperative Group (ET-ROP), have addressed this issue.14

The indication for treatment is threshold ROP and the ET-ROP Study recommends treating eyes before threshold is reached because the outcome of some eyes treated once they have developed threshold disease has been poor. This may result in modification of the currently accepted treatment guidelines and offers hope for the most difficult ROP cases. Other reported trials have shown morphological variations in extreme prematurity that do not follow the previous clinical criteria.15 These findings may also lead to the need to modify the current guidelines for treatment in extreme prematurity.

Timing

Timing is critical and should be undertaken within the treatment window. This is necessarily ill-defined, and depends very much on disease severity. Thus the most severe forms of ROP should be treated within 24–48 h from the identification of ROP reaching a criteria for treatment, while less severe types of ROP may not require treatment for possibly 4–5 days. One hesitates to be specific about treatment timing, because making this judgement can be difficult.

Preparing the baby

Close supervision and monitoring throughout the procedure can best be provided in the neonatal unit. Cryotherapy and laser treatment are painful and/or lengthy procedures and good analgesia and sedation are essential. Treatment is a team effort with the support of the neonatologist. The optimal condition is for the baby to be intubated and given artificial ventilation. Full monitoring is essential during the procedure. A separate room, usually in the NICU should be used for laser treatment and safety goggles should be worn by all staff present.

Preparing the eye

This is similar to the preparation for screening.

Anaesthesia

Our preferred method of anaesthesia is morphine for premedication and anaesthesia. Followed by Pancuronium and Fentanyl immediately prior to treatment.

Procedure

Cryotherapy is applied externally through the sclera, whereas laser therapy uses both argon-green and diode wavelengths delivered through a portable indirect ophthalmoscope. Systemic complications are rare if treatment is applied with adequate anaesthesia and monitoring. Ocular complications can occur with both treatments, but are usually minor and relatively rare.

Post-operative management

No post-operative medication is required following laser treatment. Topical antibiotic ointment is applied for 5 days following cryotherapy. The retina is examined 5–7 days later by which time ‘plus’ disease should show signs of subsiding.

Retreatment

With effective treatment, retreatment is not frequently required, but if it is, it should be undertaken as soon as it is obvious that regression has not been induced, usually within 7–10 days.

Preparation for the procedure

Preparing the parents

The parents must be informed about the nature of the disorder, the risk of blindness and the expected success rate.

Long term follow-up

All infants with stage 3 disease and those who have been treated should be kept under review for at least the preschool years to monitor the development of vision, refractive status, and ocular...
motility. The incidence of strabismus is raised between around 6% to over 30%. Myopia is a well-known complication of ROP with its onset in infancy and progression during the first year after birth but with relative stability thereafter. Long-term complications include an increased risk of developing retinal detachment, which may occur at anytime of life.

Management of advanced disease

Parents will want to know if anything can be done if cryotherapy or laser treatment has failed to stop the progression of the disease. There are a number of aspects to consider.

Vitreoretinal surgery

This is a most controversial topic. Anatomical retinal alignment can be obtained in a significant proportion of cases, but to date the visual results are extremely dismal with almost all infants gaining no improvement with respect to vision. With such poor results, surgical management cannot be recommended and it is critical that during any discussion parents are made aware of the difference between anatomical and functional success. It should be pointed out that complex surgery may put any residual useful vision at risk and leave a painful eye that requires long-term pain control. Multiple operations may be required, which impacts the psychological development of the infant.

Stage 5 ROP

These cases can develop secondary closed angle glaucoma due to anterior displacement of the iris-lens diaphragm leading to buphthalmos, band keratopathy and a cosmetic problem. Complications can be prevented by early trans-corneal lensectomy in cases with signs of anterior chamber obliteration.

Conclusion

Over the past 20 years a condition that was considered to be untreatable has become treatable with remarkable success. However, developments in neonatology have resulted in increasingly ever more premature infants surviving. This has resulted in a new patient population born extremely premature and characterised with a more severe form of ROP with its own morphological character-

istics that is more difficult to manage. Recently there have been tremendous strides in the neonatal and ophthalmic management of the preterm baby. While significant reductions in the disease have occurred further research is required to fully understand and prevent the disease.

Research directions

- Vascular development of the retina and implications for retinopathy of prematurity (ROP)
- Medical management of the baby especially the most appropriate level of oxygen required to reduce ROP
- Wide-field digital retinal imaging and the future role of telemedicine
- Optimum timing of treatment
- Better understanding of disease morphology and progression in very low birth weight infants

References


