Best Practice Guideline Article

Treatment of retinopathy of prematurity

David Clark*, K. Mandal

Aintree NHS Hospitals Trust, UK

Abstract

Retinopathy of prematurity is a potentially blinding disorder of premature infants. Retinal ablation of the avascular retina originally described using cryotherapy but now most commonly undertaken with laser photocoagulation, reduces the unfavourable structural outcomes and improves the functional visual acuity outcome. The CRYO-ROP study showed the long-term benefit of treatment of threshold disease compared with no treatment, however even with cryoablation 44.4% of treated eyes had a visual acuity of 6/60 or worse at 10 year follow-up. The ETROP study of earlier treatment for high-risk pre-threshold disease, rather than treatment at threshold, has shown that pre-threshold treatment of type 1 disease produces a significantly improved outcome. Despite treatment some infants develop retinal detachment for which various surgical treatments have been described, although not always with a good functional outcome. Future treatment modalities may include the use of anti-VEGF therapies.

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Keywords
Retinopathy of prematurity; Cryotherapy; CRYO-ROP; Laser photocoagulation; ETROP

Contents
1. Treatment modalities ..................................................... 97
2. Anti-VEGF therapies ...................................................... 98
3. Gene therapy .......................................................... 98
4. Key guidelines ......................................................... 98
5. Research directions ...................................................... 98
References .............................................................. 98

Retinopathy of prematurity (ROP) is a proliferative disease of the retinal vasculature in premature infants that may cause severe visual loss, and it is a major cause of blindness in newborns [1-3]. The disease is characterized by proliferation of abnormal fibrovascular tissue at the border of vascularised and non-vascularised retina [4]. Timely recognition of the disease is important because of the short window of opportunity during which treatment is effective [5].

In the late 1960s xenon arc photocoagulation and transcleral cryotherapy were used for the treatment of acute ROP [5,6]. The Multicentre Trial of Cryotherapy for Retinopathy Of Prematurity (CRYO-ROP) for the first time established the beneficial effect of cryoablation of the peripheral

* Corresponding author.
E-mail address: DAVID.CLARK@aintree.nhs.uk (D. Clark).

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avascular retina [7]. This has been shown to significantly reduce the progression of threshold ROP at which stage the risk of blindness if untreated is 50%. Threshold ROP is defined as 5 consecutive or 8 cumulative clock hours of extra-retinal fibrovascular proliferation, in zone I or II, in the presence of plus disease (dilated and tortuous posterior vessels, progressing to vitreous haze and pupil rigidity).

23 centres in the USA participated in the CRYO-ROP trial and 9751 infants of birth weight less than 1251 g were enrolled. The infants underwent ophthalmic examinations from 6 weeks postnatally which continued fortnightly until retinal vascularisation was complete. Of the enrolled infants, 291 that progressed to threshold disease participated in the randomized trial and were randomly allocated to have either cryotherapy, which was performed within 72 h, or to control groups.

An unfavourable outcome was defined as posterior retinal detachment, retinal fold involving the macula or retrolental tissue. Cryotherapy significantly reduced the unfavourable structural outcome of threshold ROP to 49.3% at 3 months [7,8] and 45.8% at 12 months [9]. At 12 months the risk of unfavourable structural outcome was 45.8% [9]. The beneficial effect of treatment has persisted long-term; at 10 year follow-up there was a 43.2% reduction in unfavourable structural outcome [10] and at 15 years, 30% of treated eyes and 51.9% of control eyes (P<0.001) had unfavourable structural outcomes [11].

Visual function was assessed at 3 months and 1 year using the acuity card which measured the monocular grating acuity [12]. In 95% of infants the procedure was attempted and it showed that treated infants had significantly better visual acuity than controls [9]. For the 5 1/2 year outcome study, the Early Treatment of Diabetic Retinopathy chart was used to obtain visual acuity scores and the rate of unfavourable visual acuity at this stage was 47.1% in the treated group compared to 61.7% in the controls [13]. At 10 year follow-up, 25.2% of treated eyes achieved visual acuity of 20/40 or better, compared to 23.7% of controls [10]. Unfavourable visual acuity outcomes were found in 44.7% of treated eyes and 64.3% of control eyes (P<0.001). A 15 year follow-up of the cryotherapy group revealed that even in eyes with good structural outcome, new retinal detachments could develop after 10 years highlighting the need for long-term follow-up of eyes with threshold disease [11].

Various studies, using the same treatment criteria as in the CRYO-ROP study, have demonstrated that indirect laser photocoagulation is at least as effective as cryotherapy in preventing the unfavourable outcomes of ROP [14-26].

Despite treatment the CRYO-ROP 10-year follow-up showed that 44.4% eyes had visual acuity of 6/60 or worse with eyes treated with zone I disease having significantly worse structural and visual outcome compared to eyes treated with zone II disease [10]. This led the investigators to question the criteria for treatment, i.e. was the threshold set for treatment of ROP too high especially for zone I disease? These issues were addressed in the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) study and the Early Treatment of ROP (ETROP) study.

30 centres participated in the STOP-ROP study over 5 years [27]. The aim of this study was to assess if progression to threshold disease and therefore the need for treatment could be reduced by the use of supplemental oxygen. Premature infants with pre-threshold ROP in at least one eye and pulse oximetry reading of <94% saturation were randomly assigned to the conventional arm with pulse oximetry aimed at 89-94% saturation (325 infants) or supplemental oxygen arm with pulse oximetry aimed at 96-99% saturation (324 infants). The rate of progression to threshold disease in the supplemental oxygen group (41%) was not statistically significant compared to the conventional group (48%). Supplemental oxygen also did not significantly reduce the number of infants having retinal ablative surgery.

Increased risk of adverse pulmonary events such as pneumonia and chronic lung disease was observed in the supplemental oxygen group.

26 centres in the USA participated in the ETROP study that was designed to detect if some eyes with ROP of less than threshold severity could benefit from treatment [28]. Pre-threshold was defined as:

1. Zone I, any ROP less than threshold
2. Zone II, stage 2 with plus disease and stage 3 without plus disease
3. Stage 3 with plus disease but less than threshold.

This study used a risk model (RM-ROP2) to predict the likelihood of eyes with pre-threshold ROP progressing to retinal detachment. Eyes that were at >15% risk of progressing to have unfavourable outcome were designated as the ‘high-risk pre-threshold’ eyes. They were then randomized to the early treatment group or the conventional treatment group (treatment at threshold severity). Treatment was peripheral retinal ablation. 401 of the 499 with high-risk ROP participated in the randomized trial. Masked testers measured the primary outcome (visual acuity) using Teller acuity card. Structural outcomes were assessed at 6 and 9 months. Unfavourable structural outcome at 9 months reduced from 15.6% to 9.0% (P<0.001) for the early treatment group. Unfavourable visual acuity outcomes showed a reduction from 19.5% to 14.5% (P<0.005).

There were some shortcomings of earlier treatment with more frequent systemic complications such as apnea and bradycardia in the early treatment group than in the conventional treatment group which was attributed to the young age at treatment. Ophthalmic complications were similar in the two treatment groups. Though the potential deleterious effect of early treatment on visual field was not assessed, the authors accepted that treatment of zone I disease would result in greater visual field loss than treatment of zone II disease. ETROP noted that some eyes with high-risk pre-threshold disease would undergo spontaneous disease regression and they devised a clinical algorithm based on the International Classification of ROP to identify the eyes at highest risk which would benefit from early treatment, and those that could be observed.

Type 1 ROP:
1) Zone I, any stage of ROP with plus disease;
2) Zone I, stage 3 without plus disease; or
3) Zone II, stage 2 or 3 with plus disease.

These eyes have highly active ROP and should be considered for early treatment.

Type 2 ROP:
1) Zone I, stage 1 or 2 without plus;
2) Zone II, Stage 3 without plus.

These eyes may be followed conservatively unless they progress to pre-threshold type 1 ROP or reach threshold.

Using the ICROP-based algorithm the study calculated that 8% of infants with birth weight less than 1251 g would require treatment, an increase from an estimated 6% using conventional threshold guidelines.

The updated classification of ROP has highlighted the concept of a virulent retinopathy that warrants aggressive management [29]. They describe aggressive posterior ROP (AP-ROP), usually observed in the lowest-birth-weight infants, which is characterized by its posterior location, prominence of plus disease, and the ill-defined nature of the disease. If untreated, it usually progresses to stage 5 ROP. AP-ROP is most commonly seen in zone I, but it may also occur in zone II. There is marked dilatation and tortuosity of vessels in the posterior pole in all four quadrants with shunts between vessels within the retina. Haemorrhages may occur at the junction of the vascularised and avascular retina. This disease progresses circumferentially, rapidly and it usually does not progress through the classic stages 1 to 3. AP-ROP may also appear only as a flat network of neovascularisation at the deceptively featureless junction of the vascularised and non-vascularised retina that may be missed by the inexperienced examiner.

1. Treatment modalities

Retinal cryotherapy and laser photocoagulation have both proven to be successful methods of treating active ROP. They are used to ablate the avascular retina anterior to the fibrovascular ridge.

Cryotherapy was the mode of treatment in the absence of portable laser machines. It usually requires a general anaesthetic or sedation and ventilation. Conjunctival dissection is needed in posterior disease to enable access with the cryo probe. Complications are lid edema, laceration and haemorrhage of conjunctiva, preretinal and vitreous haemorrhage.

In the past decade portable indirect laser photocoagulation has supplanted cryotherapy as the standard treatment modality of treating threshold ROP. It can be performed either under a general anaesthetic, with intubation and sedation or with a sub-tenons block. Indirect laser photocoagulation is more convenient and technically easier to administer and is of particular advantage over cryotherapy in treatment of posterior disease. It permits a precise and relatively atraumatic delivery of treatment with less ocular and systemic adverse effects. It avoids lesions to the external eye surface and sclera. The complications reported with laser are cornea, iris and lens burns, hyphaema, retinal haemorrhages and choroidal rupture. Diode red (810 nm) is preferable to argon green (514 nm) because it is less likely to cause lens opacity when using argon green laser which is less likely with diode red laser treatment.

A comparison of laser photocoagulation with cryotherapy for threshold ROP at 10 years has suggested better structural and functional outcome for eyes undergoing laser [31]. According to the results of this study, cryotherapy was associated with 7.2 times more retinal dragging than laser photocoagulation. Eyes treated with laser had mean best corrected visual acuity (BCVA) of 20/66 compared with 20/182 in eyes treated with cryotherapy [31]. Laser treated eyes have a refractive advantage as they are significantly less myopic than those treated with cryotherapy. When patients undergoing randomized bilateral treatment (cryo vs laser) were compared, the mean spherical equivalent (SE) of eyes with laser treatment was −4.48 D compared with mean SE of −7.65 D for eyes that had undergone cryotherapy [32].

A retrospective non-randomized controlled trial has shown that a dense pattern of laser photoacoagulation (649 spots for zone II disease and 1253 spots for zone I) was more successful than a less dense pattern (457 spots for zone II disease and 592 spots for zone I) in reducing disease progression [33]. It has been suggested that a more thorough ablation of the hypoxic avascular retina decreases the angiogenic factors. A near-confluent pattern of laser photoacoagulation has been recommended to minimize the rate of progression of threshold retinopathy and therefore reduce re-treatment rates [34]. The number of laser burns applied is a useful guide to the amount of treatment, but more important is adequate coverage. There is not a direct correlation between area covered and number of laser burns applied as the size of the laser burn varies depending on the distance of the aspheric lens from the eye, dioptoric power of the lens, burn intensity and duration.

Laser burns placed approximately 0.25 burn width apart, will expand to produce a near-confluent pattern [34]. Re-treatment may be necessary in eyes with persistent plus disease, active stage 3 disease, a high ridge or localized tractional detachment and diode laser photoacoagulation posterior to the ridge useful in such cases [35]. Anterior segment ischaemia and phthisis has been reported following confluent laser and cryotherapy for threshold ROP [36]. To reduce the risk of producing anterior segment ischaemia caused by ablating the long ciliary arteries it has been suggested that there should be more space between laser burns, or cryo-spots rather than confluent treatment, in the clock hours of the horizontal meridian [36].

Some infants develop retinal detachments (RDs) despite timely and thorough ablation which usually have poor anatomic and visual prognosis [10,37,38]. The risk of progressing to stage 4 ROP can be predicted by persistent vitreous haze, ridge elevation of 6 or more clock hours, and two or more quadrants of plus disease, whilst neovascularisation was not a predictor of progression to stage 4 ROP [39]. Although several operations to treat such cases have been described, there is no randomized prospective data to guide management. The various procedures described are open-sky vitrectomy, [40,41] scleral buckling procedures (SBPs), [42-51] closed vitrectomy and lensectomy with or without SBPs [52-57]. More recently lens sparing vitrectomy (LSV) without scleral buckling for partial RDs have been advocated by some authors [58-63].

Vitreous traction tends to begin in the area of the ridge and extend both circumferentially and anteroposteriorly. SBPs do not adequately address vitreoretinal tractional forces, and they require a secondary procedure to divide or remove the encircling band which allows the eye to grow normally. Unilateral SBPs induce severe myopia, anisometropia and may lead to amblyopia which ultimately limits functional success. By interrupting the involution of this vitreous traction, LSV is thought to interrupt the progression of tractional retinal detachment. The anatomic success rate for LSV is approximately 90% [46-48,55,58,60-62] compared to 60-75% [45-48,55] using SBPs. The visual results of LSVs is encouraging but can be variable [61]. The potential
complications of LSV are endophthalmitis (which has not been reported),iatrogenic retinal tears, cataract formation and glaucoma. Cataract formation is uncommon following vitreous surgery in infants with a reported rate of 5–15% in infants undergoing LSV [64,65]. Despite anatomical success there may be poor functional outcome and the eye may need further surgery for uncontrolled intraocular pressure. It is therefore critical to discuss and explain to parents the difference between structural and functional success.

2. Anti-VEGF therapies

VEGF is important in the development of ROP and new therapies for treating ROP are being developed using inhibitors of VEGF to block retinal neovascularisation.

Various anti-VEGF treatments have been used in a small number of patients either by intra vitreal injection or injection into anterior chamber of the eye. These have yet to be fully evaluated, but may be of use for patients with serious disease, and may be used as salvage therapy after laser or as monotherapy if anterior segment involvement makes laser treatment hazardous [66].

3. Gene therapy

Another method of producing local, ocular anti-VEGF therapy has used gene transfer via an intra vitreal injection of a control vector carrying the appropriate gene. This treatment has been reported as showing good results in animal testing but has yet to be used in humans.

4. Key guidelines

- Early treatment of type 1 ROP disease now advised
- Clinicians should be aware of AP-ROP which can rapidly progress to stage 5 disease
- Laser treatment has advantages over cryotherapy
- Even with timely and thorough treatment some infants develop retinal detachments (advanced disease)
- Surgery for advanced disease is described with variable outcomes
- Anti-VEGF therapies are new but not yet evaluated

5. Research directions

- Further studies on the use of surgery in advanced ROP with retinal detachment
- Use of anti-VEGF therapies in ROP treatment
- Gene therapy for ROP

References
