

## Trends in the management of stage 3 retinopathy of prematurity

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### Abstract

**Aims/Background**—The clinical outcome of 66 consecutive infants with stage 3 retinopathy of prematurity (ROP) is reported.

**Methods**—Thirty four infants (64 eyes) were treated with cryotherapy and 32 infants (59 eyes) underwent laser photocoagulation.

**Results**—Infants with anterior-mid zone II ROP had a high rate of disease regression whether treated by cryotherapy or laser photocoagulation. Infants with posterior zone II or zone I ROP had a 40% success rate with cryotherapy, and 87.5% when treated with laser photocoagulation.

**Conclusion**—Evolving experience and changing management policies in infants with posterior ROP has led to improved results.

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Recent advances in neonatal intensive care have seen the prognosis for premature infants improve significantly within the past two decades.<sup>1</sup> Associated with this improvement in survival is a concomitant increase in the incidence of retinopathy of prematurity (ROP).<sup>2</sup> It is better to prevent the cicatricial sequelae of acute stage 3 ROP than to treat it after it occurs.<sup>3</sup> The Cryotherapy ROP Study has demonstrated that cryoablation of the peripheral avascular retina can reduce the incidence of an unfavourable outcome in infants with threshold ROP in treated versus control eyes; 47.1% versus 61.7% for acuity and 26.9% versus 45.4% for fundus status.<sup>4</sup> Photocoagulation for ROP is gaining in popularity following the advent of indirect ophthalmoscopic delivery systems. Studies comparing laser and cryoablation in the treatment of ROP have found equal efficacy between these two modalities, with fewer complications reported with laser treatment.<sup>5–9</sup>

The outcome and clinical course of 66 consecutive infants (125 eyes) treated for ROP using cryotherapy and laser photocoagulation is described here.

### Patients and methods

The inpatient hospital records of all premature infants who received treatment with cryo-

therapy or laser photocoagulation for ROP between April 1989 and January 1995 were reviewed. The stage and location of ROP were recorded according to the International Classification of ROP. Infants had been screened on a fortnightly basis and in some cases weekly examinations were performed until threshold disease developed. Threshold disease was defined as a minimum of five contiguous or eight cumulative clock hours of stage 3 ROP in the presence of plus disease. In this report success or failure of treatment was defined on a structural basis in accordance with the Cryo-ROP study (an unfavourable outcome being defined as posterior retinal detachment, posterior retinal fold involving the macula, or retrolental tissue obscuring the view of the posterior pole).

Treatment was administered by the senior author (DIC) under general anaesthesia, with an attending neonatologist present in all cases. The pupils were dilated with 0.5% cyclopentolate and 2.5% phenylephrine. All infants were paralysed with pancuronium, ventilated on an air/oxygen mixture, and fentanyl 15 mg/kg was used for analgesia.<sup>8</sup> All infants were reviewed 10 days after treatment and if signs of regression were seen, fortnightly thereafter for up to three visits. For the purpose of our analysis, the patients were divided into two subgroups. An anterior group included all eyes with middle to anterior zone II (one eye had zone III) ROP, and a posterior group, which included eyes with posterior zone II and zone I disease. On

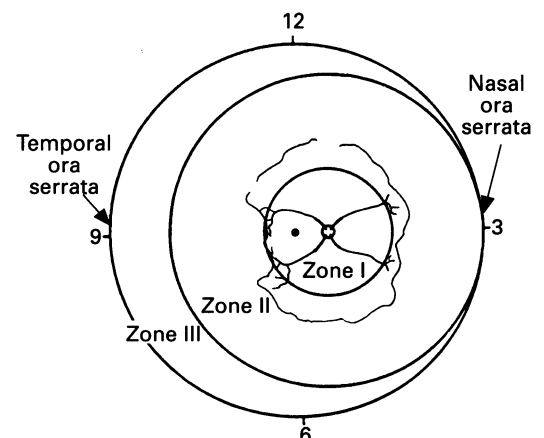


Figure 1 Infants who had retinopathy of prematurity in the posterior aspect of zone II dipping towards zone I were classified as posterior.

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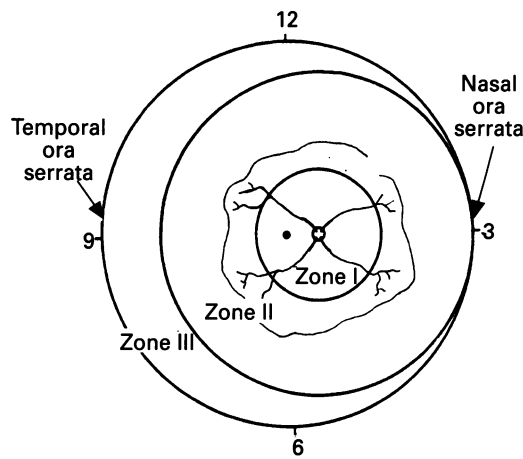


Figure 2 Anterior retinopathy of prematurity.

review of the patients' records by a 'masked' observer, infants were placed in the anterior group if there was a doubt as to whether the ROP was posterior or mid zone II (see Figs 1–3).

#### CRYOTHERAPY GROUP

Thirty four infants (64 eyes) were treated with cryotherapy, 33 of these before 1992. All patients had reached threshold disease. Cryotherapy was applied contiguously to the entire circumference of the avascular retina anterior to the edge of the ridge. One patient who had initially received diode laser photocoagulation and required retreatment, was successfully retreated with cryotherapy as the laser machine was not available. One infant required supplemental treatment with cryotherapy, but progressed to bilateral stage 5.

#### LASER GROUP

Since February 1992, 32 infants (59 eyes) were treated with either diode (nine infants) or argon laser photocoagulation (23 infants). Laser burns were placed just anterior to the ridge and in a scatter fashion throughout the remainder of the avascular retina. If plus disease persisted at follow up, re-treatment was performed within 48 hours; three infants required re-treatment in the diode group and four infants in the argon group. Three infants receiving treatment to both eyes had

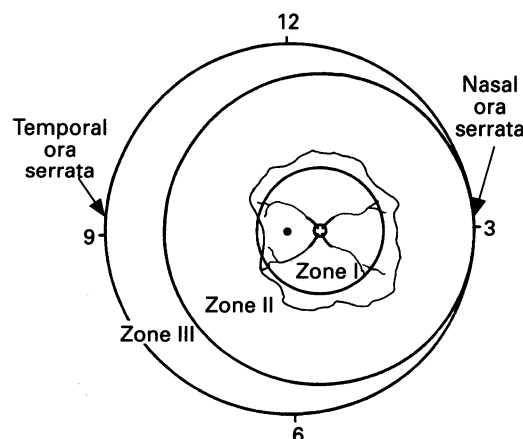


Figure 3 Posterior retinopathy of prematurity.

asymmetric disease, with threshold ROP in one eye and at least three clock hours of stage 3 ROP in the fellow eye. Another five infants with prethreshold disease in both eyes were treated with laser, three with argon, and two with diode. Of the five infants treated with prethreshold disease, two had posterior disease and three anterior disease.

#### Results

Sixty six infants with ROP were treated in this retrospective study. Cryotherapy was the mainstay of treatment from 1989 to mid 1992. Laser photocoagulation has been used from February 1992 to the present day. We compared the demographics of the two treatment groups, looking specifically at surgical results with anterior and posterior ROP (Table 1).

#### CRYOTHERAPY

Thirty four infants (64 eyes) were treated with cryotherapy, 30 eyes having posterior ROP. The median postmenstrual age at the time of treatment was 37 weeks, being somewhat less in the posterior group (36) compared with the anterior group (38). A structurally favourable outcome was achieved in 40% of the posterior group and 94% in the anterior group (Table 2). Treatment complications were seen in three infants, two infants developed an overgrowth of conjunctiva onto the cornea. This was as a consequence of the conjunctiva being incised to facilitate treatment. One other patient developed macular pigment epitheliopathy.

#### LASER

Thirty two infants (59 eyes) were treated with laser. In contrast with the cryotherapy group, only 14 eyes had posterior ROP. The median postmenstrual age at the time of treatment was also lower, being 35 weeks in the posterior group and 38 weeks in the anterior group. The demographics between the cryotherapy and laser group of infants with anterior ROP were similar. The two groups began to differ in infants with posterior ROP. Infants were born earlier and weighed less in the laser group although this was not statistically significant. The incidence of posterior ROP was significantly higher in the cryotherapy group ( $p < 0.05$ ). There was also a significant difference between the results of treatment in the posterior group ( $p < 0.03$ ). There were no systemic complications from the treatment. One infant had an acute pigment epithelial detachment which was noted immediately after treatment. This resolved spontaneously over a 2 week period.

#### Discussion

Laser photocoagulation is currently the accepted method of treatment for patients with proliferative retinopathy from disorders such as diabetes mellitus, veno-occlusive disease, and sickle cell anaemias. Cryotherapy has been

Table 1 Patient characteristics

	Posterior disease		Anterior disease	
	Cryotherapy	Laser	Cryotherapy	Laser
Treated eyes	30	14	34	45
Birth weight (g)				
Median	796	672	788	800
Range	512-950	622-920	584-1460	545-1185
Gestational age (weeks)				
Median	25.5	24	26	25
Range	24-28	23-26	24-29	23-30
Postmenstrual age at treatment (weeks)				
Median	36	35	38	38
Range	33-39	34-36	36-40	34-42
Days old at treatment				
Median	72	74	84	88
Range	65-94	69-81	75-104	39-123
No of stage 3 clock hours				
Median	10	10	7.5	6
Range	5-12	3-12	5-12	3-12

used successfully in the past to treat these disorders, but the advantage of localised laser ablation has led to the abandonment of cryotherapy in these patients except in very select cases. Now that indirect ophthalmoscopic laser treatment is widely available, the use of laser photocoagulation to treat ROP is a logical step forward from cryotherapy. Laser coagulation of the peripheral retina, when compared with cryotherapy, has less inflammation associated with it, less damage of adjacent structures, fewer systemic and ocular side effects, and technically is easier to perform when treating posterior disease. Preliminary studies indicate that laser treatment may be as effective as cryotherapy, but large numbers of patients and further clinical trials are required to reach meaningful conclusions.

The Cryotherapy for ROP Cooperative Study group found at 3½ year follow up, an overall 26.1% structural failure rate with a 45.4% functional failure rate in treated eyes with stage 3+ ROP.<sup>9</sup> This failure rate increased to 76% when the infant had zone I disease. Such failure rates in any clinical practice are unacceptably high, and ongoing studies are currently looking at ways to improve these results. Posterior disease differs from anterior zone II disease as it can rapidly progress to retinal detachment.<sup>10</sup> We have found with increasing clinical experience that infants who were at risk of progressing were recognised earlier, therefore allowing them to be followed more closely and treated in a more timely manner. The examiner can get a general impression of severity, based on several specific prognostic indicators, such as the zone in which prethreshold ROP develops, presence or absence of plus disease, the rate of progression of ROP to prethreshold, the stage of ROP, and the circumferential extent of involvement.<sup>10</sup> The improvement in our results may be attributed to the change in treatment modality, an increasing experience effect, and finally to

the treatment of prethreshold eyes in some cases. We do not know to what extent each of these three factors influenced the results. Looking at the experience factor, the laser ROP study group compared cryotherapy with laser treatment for ROP in a meta-analysis study. In their report, 80% of infants who received cryotherapy and 91% of infants who received laser treatment had a favourable outcome.<sup>11</sup> This shows an improvement in the cryotherapy results when compared with the Cryo-ROP study (73.1% favourable outcome), which may be attributed to increasing experience. Even with their increased experience the cryotherapy results fall short of those achieved with laser. The two remaining factors leading to an improvement in the results of this series are (a) treating some infants with prethreshold disease (five of 59 infants), and (b) a change in our treatment modality – that is, laser photocoagulation.

We now treat zone I disease as soon as plus disease develops. Sternberg and Tasman comment that waiting until threshold disease develops in zone I leads to a high failure rate.<sup>12,13</sup> Fleming *et al* treated 18 eyes in nine infants with posterior ROP who were prethreshold with signs of plus disease.<sup>14</sup> Disease regressed in 17 of the 18 eyes. In our study two of the eight infants with posterior disease were treated prethreshold with the diode laser, resulting in successful outcomes. Treatment of posterior disease with laser, especially zone I, was considerably easier technically and, we felt, allowed for a more complete treatment. A combination of all these factors – that is, treatment technically easier to administer, some eyes treated prethreshold, a more complete treatment, and experience gained over 6 years contributed to the improved results in this subgroup of infants with ROP. We noted that there was a significant difference between the number of eyes with posterior disease, between the group treated with cryotherapy (April 1989–June 1992), and the laser treated infants (February 1992–January 1995). We speculate that changes in the management of preterm labour and postnatal care may have contributed to this.

Six infants with anterior disease were treated prethreshold with argon laser. Three of these infants had asymmetric disease, having reached threshold disease in the fellow eye. The treatment administered in these eyes was localised to the avascular retina anterior to the area of stage 3 involvement. None of these eyes progressed to threshold, or had an unfavourable outcome. The infants with bilateral prethreshold anterior disease, had 3 to 4 clock hours of stage 3 ROP, where fibrovascular tissue had advanced a significant distance into the vitreous. Because of the risk of macular ectopia in these isolated cases, a decision to treat prethreshold was made.

Cryotherapy continues to have a role to play, as a relatively clear medium is required for treatment with laser. Any infant with vitreous haemorrhage, small pupil, or a residual tunica vasculosa lentis may not be suitable for laser

Table 2 Results of treatment (%)

	Cryotherapy		Laser	
	Posterior (30)	Anterior (34)	Posterior (14)	Anterior (45)
Successful outcome	12 (40)	32 (94)	12 (88)	44 (98)
Unsuccessful outcome	18 (60)	2 (6)	2 (12)	1 (2)
Total	30 (100)	34 (100)	14 (100)	45 (100)

treatment. Corneal haze has been reported as a complication of laser therapy, with resultant loss of focused laser delivery necessitating corneal epithelial removal for continuation of treatment.<sup>6</sup> Other anterior segment complications have been reported including cataract formation<sup>15-17</sup> and burns of the iris and tunica vasculosa lentis.<sup>18</sup> In this study the only complication seen in the laser group was an acute pigment epithelial detachment noted immediately after treatment with the argon laser. In the cryo treated group, two patients developed pterygia-type lesions after treatment and one patient developed macular pigment epitheliopathy.<sup>19</sup>

In summary, this is a clinical review of the management of ROP over the past 6 years. A direct comparison between laser and cryotherapy cannot be made, as this is a retrospective study. The improved results when treating posterior ROP with laser are encouraging. In our series anterior-mid zone ROP had a high success rate of regression whether treated with cryo or laser at threshold disease. Posterior disease usually has a poor prognosis in comparison but better results have been achieved in recent years in our group of patients. We believe the reasons were due to a combination of easier and perhaps more complete treatment achieved with laser, earlier treatment at prethreshold, and increasing clinical acumen to recognise those eyes with Rush type disease likely to have a very rapid course and poor prognosis.

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