Three year visual outcome for treated stage 3 retinopathy of prematurity: cryotherapy versus laser

I A Pearce, F C Pennie, L M Gannon, A M Weindling, D I Clark

Abstract

Background/aims—In the management of retinopathy of prematurity (ROP), several studies have demonstrated laser photocoagulation to be as effective as cryotherapy in reducing the incidence of unfavourable structural outcome. However, few data are available on the functional outcome. The 3 year visual acuity outcome of infants treated with laser or cryotherapy in a neonatal unit is presented.

Methods—The case notes of 34 infants (64 eyes) treated with cryotherapy, between 1989 and 1992, and 32 infants (59 eyes) treated with laser, between 1992 and 1995, were reviewed.

Results—In the cryotherapy group 69% of eyes had a favourable structural outcome. Of these structurally successful eyes 62.5%, 35.0%, and 33.3% of eyes had visual acuities within normal limits at the 12 month, 24 month, and 36 month corrected age milestones respectively. In the laser group 93% of eyes had a favourable structural outcome. Of these structurally successful eyes 96.4%, 66.7%, and 59.5% of eyes had visual acuities within normal limits at the 12 month, 24 month, and 36 month corrected age milestones respectively.

Conclusion—In the management of ROP, when laser photocoagulation induces a structurally successful result, the potential for normal visual acuity development at 3 years is high. Whether the poorer functional outcome of the eyes treated with cryotherapy is an artefact of the historical nature of the study or as a result of an adverse effect of the destructive trans-scleral application is unknown.

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Advances in neonatal care over the past two decades have significantly improved the prognosis for premature infants.¹ However, concomitant with improved survival rates, there has been an increase in the incidence of retinopathy of prematurity (ROP).²⁻⁴ Currently, ROP accounts for approximately 10% of childhood blindness in developed countries.^{5,6}

The multicentre, North American Cryotherapy for Retinopathy of Prematurity Study (Cryo-ROP Study) showed for the first time a convincing beneficial therapy for threshold stage 3+ ROP.^{7,8} Despite the undoubted benefits of cryotherapy in the management of threshold ROP there are certain problems.

Firstly, there can be significant ocular and systemic adverse effects of the treatment. The ocular adverse effects include conjunctival laceration, vitreous haemorrhage, and constricted visual fields while systemic complications have involved life threatening apnoea and bradycardia.⁹⁻¹¹ Secondly, 5½ year follow up of cryotherapy treated eyes shows a trend towards fewer eyes reaching a Snellen visual acuity of 6/12 or better compared with control, untreated eyes.¹² It is possible that the benefit of cryotherapy in most cases may be at the cost of the best visual potential in some cases.

With the advent of binocular indirect ophthalmoscopic delivery systems, laser photocoagulation for the management of ROP has gained in popularity over recent years. Several studies have shown both diode and argon laser therapy to be as effective as cryotherapy in threshold stage 3 ROP for reducing the incidence of unfavourable structural outcome.¹³⁻²¹ However, few data have been reported on the visual outcome for laser photocoagulation as a treatment modality in stage 3 ROP.

In this study, we have reviewed the visual outcome, at up to 3 years corrected age, of 66 infants with stage 3 ROP managed with either cryotherapy or laser photocoagulation in our unit.

Materials and methods

STUDY DESIGN

The hospital records of all premature infants who received treatment for ROP with either cryotherapy or laser photocoagulation between April 1989 and January 1995 were reviewed. The stage and location of ROP was recorded according to the International Classification of ROP.^{22,23} Threshold disease was defined as a minimum of five contiguous or eight cumulative clock hours of stage 3 ROP in zones I or II, in the presence of plus disease.⁹

CRYOTHERAPY GROUP

Between April 1989 and January 1992, 34 infants (64 eyes), all with threshold disease, were treated with cryotherapy. Cryotherapy was applied contiguously to the entire circumference of the avascular retina anterior to the edge of the ridge. Details of therapy have been described previously.²⁴

LASER GROUP

Between February 1992 and January 1995, 32 infants (59 eyes) were treated with either diode (17 eyes) or argon laser photocoagulation (42

Department of
Ophthalmology,
Walton Hospital,
Liverpool

I A Pearce
F C Pennie
L M Gannon
D I Clark

Neonatal Unit,
Liverpool Women's
Hospital, Liverpool
A M Weindling

Correspondence to:
Mr D I Clark, Department of
Ophthalmology, Walton
Hospital, Rice Lane,
Liverpool L9 1AE.

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Table 1 Demographic data

	Total		12 months		24 months		36 months	
	Cryo	Laser	Cryo	Laser	Cryo	Laser	Cryo	Laser
Infants	34	32	14	18	16	15	20	21
Eyes	64	59	23	33	27	29	33	40
Birth weight (g)								
Mean	803	829	739	817	772	788	757	824
Range	512–1460	545–1182	584–1020	545–1182	512–1082	545–1160	512–1082	545–1182
Gestational age (weeks)								
Mean	25.5	25	25.5	25	25	25	25.5	25
Range	24–29	23–30	23–26	23–30	23–28	23–30	23–28	23–30
Stage 3 clock (hours)								
Mean	8.5	7	8.5	6.9	8.6	7	8.0	6.2
Range	5–12	3–12	5–12	3–12	5–12	3–12	5–12	3–12
Zone of ROP								
Zone I (eyes)	14	4	4	2	4	2	4	2
Zone II (eyes)	50	55	19	31	23	27	29	38

eyes). Three infants receiving treatment to both eyes had asymmetric disease, with threshold disease in one eye and at least 3 clock hours of stage 3 ROP in the fellow eye. A further five infants with prethreshold disease in both eyes were treated with laser because of the posterior location of disease. Laser burns were placed just anterior to the ridge and in a scatter fashion, one burn width apart, throughout the remainder of the avascular retina. Argon laser photocoagulation was delivered using an argon green laser through a 28 dioptre lens to give a spot size of approximately 600 μm . Power sufficient to produce a dull grey/white reaction ranged from 130 to 350 mW with a pulse duration of 0.1 seconds. The mean number of burns was 1645 (range 400–3550).

Diode laser photocoagulation was delivered using a 810 nm diode laser with a 600 μm spot size. Power sufficient to produce a dull grey/white reaction ranged from 200 to 1200 mW with a pulse duration of 0.1–0.2 seconds. The mean number of burns was 804 (range 327–1441).²⁴

NEONATAL BRAIN ULTRASOUND

Many of the preterm infants had brain ultrasound scans performed during the neonatal period. These scans were reviewed by a consultant paediatrician masked to both the extent of ROP and the modality of treatment for ROP. Scans were not available for all infants, as either they were not performed or could not be traced. The nature of periventricular haemorrhage (PVH) was graded (grade 0 = normal; grade I = subependymal haemorrhage; grade II = intraventricular haemorrhage; grade III = intraventricular haemorrhage and dilatation; grade IV = parenchymal haemorrhage). The nature of periventricular leucomalacia (PVL) was graded (grade 0 = normal; grade 1 = flares; grade 2 = small cysts; grade 3 = large, widespread cysts).

VISUAL ACUITY AND REFRACTIVE DATA

Visual acuity and refraction data were analysed at the 12 month (SD 3 months), 24 month (4 months), and 36 month (6 months) corrected age milestones. The corrected age is defined as that age from the original full term date. Visual acuity testing was performed by experienced personnel using either Teller or Keeler acuity cards at a test distance of 38 cm or, particularly

for older infants, Cardiff acuity cards at a test distance of 50 cm. At the 36 month milestone some infants had vision tested using Kay pictures to give a Snellen equivalent acuity. In some infants only binocular, rather than monocular, visual acuity data were available.

At the 12 and 24 month milestones refractive errors were corrected if myopia was greater than -6.0 dioptres, hypermetropia greater than $+4.5$ dioptres, or anisometropia greater than $+2.0$ dioptres. At the 36 month milestone refractive errors were corrected if myopia was greater than -2.0 dioptres, hypermetropia greater than $+2.0$ dioptres, or anisometropia greater than $+1.5$ dioptres.

At each milestone visual acuity data were compared with available data of binocular/monocular normal visual acuity ranges for healthy full term infants.^{25–28} At the 36 month milestone the Snellen equivalent acuities obtained using Kay pictures were considered as favourable and within normal limits if 6/12 or better.²⁹ Visual acuity data were recorded as being within the normal range, within one octave or two octaves of the lower limit of normal range, or greater than two octaves from the lower limit of the normal range. In cases where vision was considered to be only perception of light or worse, owing to progression of disease to stage 4B or 5, these were categorised as unrecordable visual acuity.

Cycloplegic refraction (1% cyclopentolate) was performed by an experienced optometrist using hand held lenses in front of awake infants. The sphere, cylinder, and axis were recorded and the equivalent sphere was calculated from the formula; spherical equivalent SE = ($\pm$ sphere) + 0.5 (cylinder).³⁰

Results

During the study period, 1071 preterm infants born less than 32 weeks' gestation or less than 1500 g were screened (mean birth weight = 1238 g; mean gestational age = 29 weeks). One hundred and two infants (9.5%) had stage 3 ROP with 73 (6.8%) of these requiring treatment using either cryotherapy or laser photocoagulation. Seven of these treated infants subsequently died leaving a total of 66 infants included in this study.

Table 2 Neonatal brain ultrasound results

	Total		12 months		24 months		36 months	
	Cryo	Laser	Cryo	Laser	Cryo	Laser	Cryo	Laser
Infants	34	32	14	18	16	15	20	21
USS data:								
Unavailable (infants)	10	12	1	4	0	2	1	3
Grade III or IV PVH (infants)	5	7	2	3	2	4	3	5
Grade 2 or 3 PVL (infants)	1	1	0	1	0	1	0	1

PVH = periventricular haemorrhage; PVL = periventricular leucomalacia.

DEMOGRAPHICS

During the study period 64 eyes of 34 infants were treated with cryotherapy and 59 eyes of 32 infants were treated with laser photocoagulation. The demographics of these two treatment groups were similar in terms of birth weight, gestational age, and clock hours of disease (Table 1).

At each corrected age milestone visual acuity data were not available for all the treated eyes for a variety of reasons. For example, the infant did not attend the clinic close to the age milestone or there was poor cooperation during the acuity testing or binocular vision measurements were recorded in infants with only one eye treated. In addition, eyes that progressed to stage 4B or 5 ROP had unrecordable vision and are not included in the comparison of the visual outcome.

At the 12 month, 24 month, and 36 month corrected age milestones the demographics for each of the treatment groups are similar (Table 1).

Table 3 Refractive error

Refraction	12 months		24 months		36 months	
	Cryo	Laser	Cryo	Laser	Cryo	Laser
Mean spherical equivalent (dioptries)	-7.0	-2.5	-7.9	-3.7	-7.3	-2.2
Range	-20.38 to +0.88	-12.75 to +3.00	-22.88 to +1.25	-12.25 to +2.88	-23.25 to +1.38	-14.25 to +4.00

Table 4 Monocular and binocular visual outcomes

	12 Months		24 Months		36 Months	
	Cryo	Laser	Cryo	Laser	Cryo	Laser
Monocular acuity (n = eyes):						
Within normal range	66.7% (6/9)	95.7% (22/23)	38.5% (5/13)	73.7% (14/19)	38.1% (8/21)	64.7% (22/34)
<1 octave	11.1% (1/9)	4.3% (1/23)	30.7% (4/13)	21.1% (4/19)	38.1% (8/21)	29.4% (10/34)
1 to 2 octave	11.1% (1/9)	0% (0/23)	7.7% (1/13)	5.2% (1/19)	4.8% (1/21)	5.9% (2/34)
>2 octave	11.1% (1/9)	0% (0/23)	23.1% (3/13)	0% (0/19)	19.0% (4/21)	0% (0/34)
Binocular acuity (n = infants):						
Within normal range	57.1% (4/7)	100% (5/5)	28.6% (2/7)	40% (2/5)	16.7% (1/6)	0% (0/3)
<1 octave	14.3% (1/7)	0% (0/5)	28.6% (2/7)	20% (1/5)	66.6% (4/6)	66.7% (2/3)
1 to 2 octave	28.6% (2/7)	0% (0/5)	14.3% (1/7)	20% (1/5)	0% (0/6)	0% (0/3)
>2 octave	0% (0/7)	0% (0/5)	28.6% (2/7)	20% (1/5)	16.7% (1/6)	33.3% (1/3)

<1 octave = less than 1 octave from the lower limit of the normal range.

1 to 2 octave = between 1 and 2 octave from the lower limit of the normal range.

> 2 octave = greater than 2 octave from the lower limit of the normal range.

UNRECORDABLE VISION

In the cryotherapy treatment group, 31% of eyes (20/64) had unrecordable vision due to progression of the ROP to stage 4B or 5. In the laser treatment group 7% of eyes (4/59) had unrecordable vision due to progression of the ROP to stage 4B or 5.

ZONE I DISEASE

In the cryotherapy treatment group 14 eyes (22%) had zone I disease. In the laser treatment group four eyes (7 %) had zone I disease. Of the 14 cryotherapy treated eyes 10 progressed to stage 4B or 5 ROP with unrecordable vision. Thus, only four cryotherapy treated eyes (6%) with zone I disease had recordable vision and are included in the subsequent presentation of visual acuity data. Of the four laser treated eyes two progressed to stage 4B or 5 ROP with unrecordable vision. Thus, only two laser treated eyes (3%) with zone I disease had recordable vision and are included in the subsequent presentation of visual acuity data.

NEONATAL BRAIN ULTRASOUND

The incidences of the neonatal neurological complications of the more severe grades of PVH (grades III or IV) and PVL (grades 2 or 3) were similar between the cryotherapy treatment group and the laser treatment group (Table 2).

REFRACTIVE ERROR

At each of the corrected age milestones the eyes treated with cryotherapy were more myopic than the eyes treated with laser photocoagulation (Table 3).

12 MONTH MILESTONE

At the 12 month corrected age milestone monocular visual acuities were recorded in nine eyes in the cryotherapy group and 23 eyes in the laser group. Binocular visual acuities were recorded in seven infants in the cryotherapy group and five infants in the laser group (Table 4). When we consider both monocular and binocular measurements together then 62.5% (10/16) of recorded vision of the cryotherapy treated group were within normal limits. This compared with 96.4% (27/28) of the laser treated group with vision recorded within normal limits (Fig 1).

24 MONTH MILESTONE

At the 24 month corrected age milestone monocular visual acuities were recorded in 13 eyes in the cryotherapy group and 19 eyes in the laser group. Binocular visual acuities were recorded in seven infants in the cryotherapy group and five infants in the laser group (Table 4). When we consider both monocular and binocular measurements together then 35.0% (7/20) of recorded vision of the cryotherapy treated group were within normal limits. This compared with 66.7% (16/24) of the laser treated group with vision recorded within normal limits (Fig 1).

Figure 1 Percentage of recorded vision (monocular and binocular combined) within normal limits.

36 MONTH MILESTONE

At the 36 month corrected age milestone monocular visual acuities were recorded in 21 eyes in the cryotherapy group and 34 eyes in the laser group. Binocular visual acuities were recorded in six infants in the cryotherapy group and three infants in the laser group (Table 4). When we consider both monocular and binocular measurements together then 33.3% (9/27) of recorded vision of the cryotherapy treated group were within normal limits. This compared with 59.5% (22/37) of the laser treated group with vision recorded within normal limits (Fig 1).

COMPLICATIONS

There were no systemic complications from either cryotherapy or laser treatment. In the cryotherapy treated group, two eyes developed an overgrowth of incised conjunctiva onto the cornea and a third eye developed a macular pigment epitheliopathy following treatment. In the laser treated group, one eye developed a pigment epithelial detachment immediately following treatment. This resolved spontaneously over a 2 week period.

Discussion

The multicentre Cryo-ROP study has convincingly shown the efficacy of cryotherapy in reducing the incidence of unfavourable structural and functional outcomes for premature infants with threshold stage 3 ROP.^{7,8} However, significant ocular adverse effects, such as conjunctival laceration, vitreous haemorrhage, and constricted visual fields have been reported with this method of treatment.^{9,10} Moreover, the 5½ year follow up of cryotherapy treated eyes has shown an unanticipated trend towards fewer eyes achieving a Snellen acuity of 6/12 or better when compared with control, untreated eyes.¹² The possibility that the benefit of cryotherapy in most cases may be at the sacrifice of the best visual potential in some cases urges caution for this treatment method, particular in the management of prethreshold disease, and

stimulates the debate as to the use of laser photocoagulation.

Several reports^{19,31-34} and prospective, randomised trials^{14,15,17,18} have supported laser photocoagulation as being effective in the management of threshold ROP. Although no randomised trial has been conducted on the scale of the Cryo-ROP trial, meta-analysis of available smaller studies has shown laser treatment to be as effective as cryotherapy in achieving a favourable structural outcome in most cases.¹³ However, there are relatively few data on the functional outcome of eyes treated with laser photocoagulation.

In our study, we present the functional outcome, at up to a corrected age of 36 months, for a group of infants who received laser photocoagulation for ROP. In addition, we have compared these functional outcome data with those of a previous cohort of infants treated with cryotherapy. Although we accept all the limitations of a retrospective, historical comparison we have included these data to demonstrate the changing trends and results of our ROP management.

In our study, 6.8% of the screened infants required treatment for ROP. Although this incidence is comparable with reported incidences of threshold ROP in other studies³⁵⁻³⁸ it is four times that of a recent report by Goble *et al.*³⁹ This variation in the incidence of threshold ROP is not currently fully explained. Our series may be biased by the referral of certain preterm infants to our unit from other units although the mean birth weights and gestational ages are similar between the series. It may be that the variation in the incidences of threshold ROP between units may reflect differences in neonatal practice. Indeed, a recent study of five neonatal units (Birmingham, Leicester, Liverpool, Nottingham, and Sheffield) showed Liverpool to have not only a higher incidence of threshold ROP but also a significantly lower mortality than the other units.⁴⁰

We have previously presented structural outcomes for treatment of stage 3 ROP.²⁴ For anterior-mid zone II ROP an unfavourable structural outcome was low whether treated with cryotherapy (6%) or laser photocoagulation (2%). However, for infants with posterior zone II or zone I ROP an unfavourable outcome was more common when treated with cryotherapy (60%) compared with laser photocoagulation (12%). In this present study of functional outcomes we have not been able to categorise the two treatment groups into anterior and posterior disease as the low numbers of recorded vision at each milestone would have made the data meaningless.

The demographics of each of the treatment groups are similar in terms of birth weight, gestational age, and extent of disease (Table 1). However, eyes treated with cryotherapy were more myopic than eyes managed with laser photocoagulation (Table 3). The association between myopia and ROP has been recognised for many years.^{41,42} More recently, evidence has accumulated to suggest that cryotherapy treatment itself may contribute to the development

of myopia^{29 43} and that laser photocoagulation produces less myopic shift.⁴⁴ The data presented here and the results of a longitudinal study of refractive outcome in our unit support the hypothesis that laser treatment induces less myopia than cryotherapy.⁴⁵ The exact mechanism to account for this apparent myopic shift is unclear but may be due to the destructive effect of cryotherapy on developing sclera.^{46 47}

In this study, 93% (55/59) of the laser treated eyes had a structurally successful result with potentially recordable vision. Visual acuity was within normal limits for a high percentage of these eyes at each of the different milestones (96.4% at 12 months; 66.7% at 24 months; 59.5% at 36 months). The fluctuations in the percentages of eyes within normal limits at each of the different milestones may reflect differences in the acuity methods used, differences in the case mix at each milestone, or the dynamic nature of acuity development over this period. This last phenomenon has been previously recognised in the apparent reduction in the successful functional outcome from the 1 year to the 3½ year follow up of the treated eyes in the Cryo-ROP study.^{8 29}

If we consider just the 36 month milestone, then the functional outcome of structurally successful eyes was high with 59.5% (22/37) of recorded acuities within normal limits and 91.9% (34/37) within normal range or less than one octave from it. Our results compare well with those reported by Ling *et al* of a series of 13 babies (25 eyes) with threshold ROP treated with diode laser photocoagulation. Of 10 eyes that had been followed up at 18 months corrected age all had grating acuity within the normal range or less than one octave from it.²¹

In our present study, 69% (44/64) of the cryotherapy treated group had a structurally successful result with potentially recordable vision. The higher incidence of zone I disease and posterior zone II disease may account for the poorer structural success rate in this group compared with our laser group.²⁴ Visual acuity was within normal limits for a moderate percentage of the structurally successful eyes at each of the different milestones (62.5% at 12 months; 35.0% at 24 months; 33.3% at 36 months). Again, as with the laser group, fluctuation in the results at the different milestones is demonstrated with the 12 month data appearing the best. If we just consider the 36 month milestone, then the functional outcome of structurally successful eyes was poorer than the laser treated group with 33.3% (9/27) of recorded acuities within normal limits and 77.8% (21/27) within normal range or less than one octave from it.

The functional outcomes of the structurally successful eyes were better for the laser treated eyes compared with the cryotherapy eyes at each of the corrected age milestones (Fig 1). However, it would not be valid statistically to compare the two groups as the absence of complete data at each milestone could bias the results.

When assessing the functional outcome we have compared the results against existing nor-

mal population data and categorised them accordingly. In the case of Teller acuity cards we have used the same normal population data as that used in the Cryo-ROP study. Although further normal population data have been published more recently, with 12 month data spanning higher spatial frequencies, the data for the 24 month and 36 month milestones were similar to the original data.^{48 49}

There are several possible reasons why the functional outcome of the laser treated group is better than our cryotherapy treated group. Firstly, the change in treatment from cryotherapy to laser over recent years has coincided with advances in prenatal and neonatal care. It is not known how the changes in the use of surfactant, the administration of maternal steroids during pregnancy, and parenteral nutrition might affect the ocular and visual pathway development and thus lead to improved visual functioning. However, the incidences of severe grades of the perinatal neurological complications of PVH and PVL, that have been shown to be associated with visual loss,⁵⁰ were similar between the cryotherapy treatment group and the laser treatment group (Table 2). Another factor that may have influenced the results is that some of the laser treated eyes were treated at a prethreshold level and thus may have had the potential for a better visual outcome. A further factor that might have affected the results is the higher incidence of myopia in our cryotherapy group. Refractive errors were only corrected if myopia was greater than -6.0 dioptres at the 12 month and 24 month milestones and if greater than -2.0 dioptres at the 36 month milestone. Although acuity cards were held at near test distances there would still have been an element of undercorrection of myopia particularly at the 12 month and 24 month milestones. As preferential looking is very sensitive to visual blur we may have underestimated the functional outcome in the cryotherapy group.

A final factor that may have influenced the outcome is the possible deleterious effect of cryotherapy on the sclera, choroidal blood flow, and retinal pigment epithelium. Several reports have demonstrated pigment epitheliopathy and choroidal thinning at the macula in eyes treated for ROP with cryotherapy that subsequently develop poorer visual outcome.^{51 52} Serous retinal detachment, pigment dispersion, and changes in choroidal blood flow have all been postulated to account for the macular changes but the exact mechanism remains unknown. It may be that the macular changes induced by cryotherapy account for some of the eyes in the Cryo-ROP study not reaching their best potential vision when compared with untreated control eyes.¹² Only one of our cryotherapy treated eyes had a macular pigment epitheliopathy noted but it is possible that subclinical changes were present in other eyes.

In summary, this report demonstrates that in the management of ROP when laser photocoagulation induces a structurally successful result the potential for normal visual acuity development is high. In addition, cryotherapy

appears to induce more myopia than laser photocoagulation although the mechanism accounting for this is unknown. The better functional outcome with laser compared with cryotherapy may reflect subtle adverse effects on ocular development induced by the transcleral destructive nature of cryotherapy. However, the current study is unable to completely exclude the possibility that the observed differences were due to changes in neonatal care of these infants or the treatment of prethreshold disease.

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