

Advanced cicatricial retinopathy of prematurity – outcome and complications

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Abstract

Aims—To assess the outcome and complications of patients with advanced retinopathy of prematurity (ROP).

Methods—All patients with eyes achieving stage 4 or 5 retinopathy of prematurity were reviewed. Twenty one eyes were diagnosed during ROP screening in maternity hospitals and 10 eyes were of infants transferred for treatment.

Results—Thirty one eyes of 17 patients were included. Thirteen eyes were treated for acute disease but progressed to stage 4 or 5; seven had cryotherapy and six diode laser photocoagulation. Cataract was found in 17 eyes (54.8%), glaucoma in seven eyes (22.6%), microphthalmos in 15 (48.4%), and corneal opacification in four eyes (12.9%). Fifteen eyes had surgical procedures; two (6.5%) had trabeculectomy, four (12.9%) had lensectomy, and nine (29%) retinal detachment repair. Transferred infants had their initial eye examination later than infants in hospitals screened by the authors and 80% of them had progressed beyond threshold ROP by the time they were transferred for treatment. Twenty nine eyes (93.6%) had visual acuities of 3/60 or less and only two eyes (6.5%) achieved 6/18 or less.

Conclusion—The visual outcome of the eyes undergoing retinal re-attachment surgery was disappointing. Cataract, microphthalmos, and glaucoma were the most frequent complications, and surgical intervention was often required. The need for children who are blind as a result of ROP to have long term follow up is shown.

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Although the multicentre trial of cryotherapy for retinopathy of prematurity showed that treatment of threshold disease (stage 3 acute ROP in zones 1 or 2, for eight cumulative or five contiguous clock hours, with plus disease) with cryotherapy results in a 50% decrease in unfavourable outcomes, a significant number of cases progress from threshold disease to stages 4 and 5 – that is, partial or total retinal detachment.¹ A previous study by Robinson and O'Keefe found an incidence of poor visual outcome (vision <6/60) in 56% of eyes reaching stage 3 disease and an incidence of total retinal detachment of 6.5%.² This study examines the incidence of complications and the structural and visual outcomes of infants with grade 4 and 5 cicatricial retinopathy of prematurity.

Materials and methods

All patients with a diagnosis of grades 4 and 5 cicatricial retinopathy of prematurity (ROP) attending the eye clinic at The Children's Hospital were reviewed. Eyes which achieved stage 4 or 5 ROP during the acute stage were selected. Thirty one eyes of 17 patients were included in the study and the mean follow up was 4.68 (range 1 to 9) years.

Twelve patients (21 eyes) were diagnosed during screening at maternity hospitals in Dublin while five patients (10 eyes) were diagnosed elsewhere and transferred to The Children's Hospital for treatment. All eyes were treated by the same surgeon (MO'K). During follow up all eyes had microscopic examination of the anterior segment, fundus examination with the binocular indirect ophthalmoscope, intraocular pressure measurements with a Perkin's tonometer, and corneal diameter measurements with callipers, as well as retinography and ultrasound scans where applicable. Microphthalmos was taken as an ultrasound A-scan (or B-scan) finding of a globe size smaller than that expected for the age of the infant.

Visual acuities were tested by the following methods depending on the age of the patient: (1) fixation, (2) forced choice preferential looking, (3) Kay's pictures, (4) Sheridan Gardner singles, or (5) Snellen chart.

The fundus examinations during the acute stages were recorded on standard forms following the International Classification of Retinopathy of Prematurity (ICROP) criteria.

Statistical analysis was carried out with the EPI INFO software package and for comparison of proportions the Kruskal-Wallis H test was used.

Results

Thirty one eyes of 17 patients were included in the study. The mean gestation of the patients was 26.77 (range 24 to 30) weeks and the mean birth weight was 951.43 (range 600 to 1500) g. The mean postnatal age at the first eye examination was 12 (range 6 to 36) weeks or 39 weeks postmenstrual age (range 30 to 60) weeks (see Table 1). Transferred infants had a significantly lower mean gestational age than infants diagnosed in hospitals screened by the authors ($p=0.04$). The mean birth weight of transferred infants was also lower than that of the non-transferred infants but this was not statistically significant ($p=0.6$). The mean postnatal age at first eye examination was significantly greater in transferred versus non-transferred infants ($p=0.009$) and 80% (4/5) of the transferred infants were already stage 4

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Table 1 Mean gestational age, mean birth weight, and mean age at first eye examination

	Mean gestation (weeks)	Mean birth weight (g)	Mean postmenstrual age first seen (weeks)	Mean postnatal age first seen (weeks)
Transferred infants	25.2 (24-30)	875 (660-1000)	46 (36-60)	21 (11-36)
Screened maternity hospital*	27.42 (24-30)	982 (600-1000)	35.83 (30-54)	8 (6-26)
Both groups	26.77 (24-30)	951.43 (600-1500)	39 (30-60)	12 (6-36)

*Screened maternity hospital=hospitals screened by the authors.

or 5 versus 42% (5/12) of the non-transferred infants.

Seventeen eyes (54.8%) had stage 4 or 5, or cicatricial retinopathy at the initial examination and 14 eyes (45.2%) had pre-threshold or threshold disease but progressed to stage 4 or 5 retinopathy. Eight eyes out of 14 in the latter group had stage 3 disease in posterior zone 2. Nine eyes which progressed to stage 4 or 5 had retinal detachment repair (Table 2). Thirteen eyes (41.9%) were treated for acute disease, seven (22.6%) with cryotherapy, and six (19.4%) with diode laser photocoagulation. The remaining 18 eyes (58.1%) were not treated. The mean postmenstrual age of first treatment was 35.64 (range 31 to 38) weeks.

Cataract was found in 17 eyes (54.8%), glaucoma in seven eyes (22.6%), microphthalmos in 15 eyes (48.4%), and corneal opacification in four eyes (12.9%).

Surgical procedures were carried out in 15 eyes (48.4%, Table 2). Two eyes (6.5%) had trabeculectomy, one (3.2%) had neodymium-yttrium-aluminium-garnet (Nd-YAG) laser peripheral iridotomies and four (12.9%) had lensectomy for control of glaucoma. Nine eyes (29.0%) had retinal detachment surgery, seven had closed vitrectomy/lensectomy, and two had encircling band only.

Following retinal reattachment procedures, uncentral, unsteady, unmaintained (UCUSUM) vision by fixation was obtained in two eyes, perception of light (PL) was obtained in two

Table 2 Surgery, retinal outcome, and visual acuity

Eye No	Type of surgery	Retinal outcome	Vision
1	Trabeculectomy	Retrolental mass	NPL
2	Trabeculectomy	Retrolental mass	NPL
3	Lensectomy	Retrolental mass	NPL
4	-	Retrolental mass	NPL
5	YAG peripheral iridotomies	Total RD	PL
6	-	Subtotal RD	6/18
7	Lensectomy	Total RD	NPL
8	Scleral buckling	Total RD	PL
9	-	Retrolental mass	UCUSUM
10	Lensectomy, vitrectomy	Retrolental mass	NPL
11	-	Retrolental mass	NPL
12	-	Total RD	PL
13	-	Total RD	PL
14	-	Total RD	NPL
15	-	Peripheral RD, macula on	4/60
16	Lensectomy, vitrectomy	Partial RD, macular band	NPL
17	Lensectomy, vitrectomy	Subtotal RD, posterior pole on	NPL
18	Scleral buckle	Total RD	UCUSUM
19	-	Total RD	UCUSUM
20	Lensectomy, vitrectomy	Retrolental mass	NPL
21	Lensectomy, vitrectomy	Partial RD, macular band	PL
22	-	Dragging macula, disc	3/60
23	-	Dragging macula, disc	3/60
24	-	Retrolental mass	UCUSUM
25	Lensectomy, vitrectomy	Retrolental mass	UCUSUM
26	-	Retrolental mass	UCUSUM
27	-	Retrolental mass	UCUSUM
28	Lensectomy	Retrolental mass	UCUSUM
29	Lensectomy	Macular fold, RPE change	PL
30	Lensectomy, vitrectomy	Partial rhegmatogenous RD	NPL
31	-	Total RD	NPL

RD=retinal detachment, PL=perception of light, NPL=no perception of light, UCUSUM=uncentral, unsteady, unmaintained.

eyes, and the remaining five eyes had no perception of light (NPL). Five of these retinas were totally detached and four partially at the last funduscopy. Of the latter, two had a macular tractional band with a partial detachment, one had part of the posterior pole only attached, and one developed a rhegmatogenous detachment with a large hole post-operatively.

Visual acuities attained in the cohort were 3/60 Snellen (or equivalent) or less in 29 eyes (93.5%); NPL in 13 eyes (42%), PL in six (19.4%), UCUSUM in eight (25.8%), and 3/60 in two (6.5%). Acuities of better than 3/60 to 6/18 were recorded in only two eyes (6.5%).

Discussion

Despite advances in treatment of acute ROP – namely, cryotherapy and laser photocoagulation, approximately 25% of eyes treated for threshold disease progress to unfavourable outcomes as defined by the multicentre trial of cryotherapy for retinopathy of prematurity (Cryo-ROP).¹ Similarly, Landers *et al*³ found 27% of eyes had an unfavourable outcome using the argon laser. McNamara *et al*,⁴ Hunter and Repka,⁵ and Goggin and O'Keefe,⁶ found the diode laser to be equally as effective as cryotherapy for treatment of threshold ROP.

Although the literature cites that encouraging anatomical results are obtainable by vitreoretinal surgery,⁷⁻¹⁰ the visual outcome remains poor.^{7 8 11 12} Trese¹³ found that scleral buckling decreased the incidence of progression from stage 4 to stage 5 ROP by reducing the vitreous traction and allowing the retinal pigment epithelium to absorb subretinal fluid, thus facilitating retinal reattachment.

Greven and Tasman⁹ found that scleral buckling resulted in anatomical reattachment in 59% in a series of 22 eyes with traction retinal detachment secondary to ROP. Machemer and deJuan¹⁰ felt that scleral buckling should be tried first in stage 4B where tractional detachment involves the macula. For high detachment and where vitreous opacities were present they advocated closed vitrectomy. Zilis *et al*⁷ found that the preoperative configuration of the stage 5 retinal detachment was of prognostic importance with wide-wide funnel configurations having the best prognosis and narrow-narrow the worst.

In this study, both the anatomical results and the visual outcome of vitreoretinal surgery were disappointing. Seven of these cases had closed vitrectomy with lensectomy while two eyes had an encircling band only.

Microphthalmos was present in 48.4% of cases in this study. Previously, Pulido *et al*¹⁴ found that axial length measurements in eyes with ROP were significantly smaller than normal. Kelly and Fielder¹⁵ felt that microcornea was due to failure of growth of the globe during severe acute ROP. Laws *et al*¹⁶ showed that axial length of the globe is inversely related to increasing stage of ROP and found a trend towards slower rates of growth in eyes that

reached stage 3 than in non-ROP eyes. This is in keeping with our impression that failure of globe growth occurs in eyes with significant ROP.

Glaucoma was present in 22.6% of eyes in this series. Various mechanisms have been reported in the pathogenesis of glaucoma in infants with stage 5 ROP. Contraction of the retrolental mass with forward movement of the lens-iris diaphragm is thought to be the most likely mechanism.^{17 18} Secondary angle closure glaucoma then occurs which can be managed medically – by lensectomy, by peripheral iridectomy/iridotomy (PI), by tube shunt implantation, by cilio-destructive procedures, by trabeculectomy, or by a combination of these. Rubeotic glaucoma may also occur which may be managed by shunt implantation in eyes with vision or by cilio-destructive procedures in blind eyes.

In the seven patients in this cohort, the glaucoma was due to pupillary block, resulting in angle closure glaucoma. There is forward movement of the lens-iris diaphragm, shallowing of the anterior chamber, and the formation of peripheral anterior synechiae and posterior synechiae in these chronically inflamed eyes.

Cataract was found in 54.8% (17 eyes) in this study. Glaucoma frequently co-exists with the lens opacities and lensectomy is one method of treating the glaucoma.¹⁹

Removal of the lens was a very important aspect of management in our seven glaucoma cases. We successfully managed glaucoma in four eyes by lensectomy, in two eyes by trabeculectomy, and in one eye by PI.

In addition to glaucoma and lens opacities, the presence of chronic low grade inflammation also results in the formation of band keratopathy and corneal scarring. Eye rubbing in children with visual impairment due to advanced ROP also contributes to the corneal scarring.

Transfer of the baby from another hospital was associated with increasing age at initial eye examination (for transferred infants, the age of initial eye examination was obtained from information in the referral letter or notes accompanying the patient). Significantly more infants were first seen at or later than 8 weeks postnatal age ($p=0.009$) in the transferred group. The mean postmenstrual age at initial eye examination for transferred infants was 46 weeks (range 36 to 60 weeks) and only two eyes were treatable at this stage with cryotherapy or diode laser (Table 1). The initial eye examination for the remaining infants took place at 6 weeks postnatal age during screening in maternity hospitals except for three infants who were seen later than recommended in the protocol.

The study shows the need for long term follow up in children who are blind from ROP. It highlights the main complications which may occur, many of which need active management. We found that the results in vitreo-retinal surgery on eyes with stage 4 and 5 ROP were disappointing and this highlights the need

for better preventive measures or more effective management of the acute phase. The study illustrates the need for further training in screening in peripheral units or else a change in policy to transfer all infants with acute ROP to main centres before they achieve threshold disease.

The Cryo-ROP study found that zone 1 location of ROP carries an 8.24 times greater odds of proceeding to an unfavourable outcome than does location in zone 2.²⁰ We found that 57% (eight of 14) of eyes in this study which initially had pre-threshold or threshold ROP, had stage 3 disease in the posterior area of zone 2. Although we do not know the true incidence of treatment failure in posterior zone 2 for this sample, this finding supports the previous report that more posterior location of ROP is associated with a poorer outcome. We should revisit the concept of threshold disease, particularly in zones 1 and posterior zone 2, in terms of whether earlier treatment is required when ROP is located in these more posterior areas of the retina.

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