Cryotherapy for retinopathy of prematurity – a prospective study

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Abstract
Cryotherapy has been shown to reduce the unfavourable outcome in retinopathy of prematurity with stage 3 threshold disease by 50%. In a prospective study cryotherapy had a favourable outcome in 13 of 24 eyes with stage 3 threshold disease. The visual outcome, refraction, and complications of cryotherapy are discussed.

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness.[1][2] Cryotherapy was first used in the treatment of this condition in the 1970s.[3][4][5][6] However the methods of application and the overall success rate differed.[7][8][9][10] To standardise treatment the multicentre North American Cryotherapy for Retinopathy Study Group trial (CRYOROP) was established in 1986 and the results, published in 1988,[11] showed that the incidence of an unfavourable outcome could be reduced from 43% to 21·5% in treated cases. We present our own experience and results in a prospective study of children treated since 1986.

Materials and methods
All infants born between January 1986 and December 1990 with documented ROP who attended the Children's Hospital, Dublin are included in a prospective study to monitor the long-term effects of premature birth and ROP. Sixteen premature infants (nine male and seven female) who received cryotherapy in this study form the basis for this paper.

Our indications for treatment were based on the criteria defined by the CRYOROP group – that is, stage 3 threshold disease, defined as stage 3+ disease involving five contiguous or eight cumulative 30 degree sectors in zone 1 or zone 2. However we differed from the CRYOROP trial in that we treated both eyes in some infants and stage 4a in one child. Under direct visualisation, using the indirect ophthalmoscope and a cataract probe, cryopexy was applied separately but contiguously for 2–6 seconds until a blanching effect was seen. Treatment was applied to the avascular retina from the ridge to the ora serrata, excluding the ridge. Cryotherapy varied from five consecutive or eight cumulative sectors, as defined by CRYOROP, or involved the whole circumference depending on the severity of ROP. The procedure was carried out in the operating theatre under general anaesthesia. The infants ranged in age from 6–15 weeks at the time of treatment.

Follow-up ranged from 3 months to 5 years. Visual acuity was recorded by fixation pattern, forced choice preferential, Allen's picture cards, or Sheridan Gardiner, depending

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on the ability of the child. Refraction and other eye abnormalities were also recorded.

Results
Thirteen eyes regressed to normal with peripheral cryotherapy scars only, 11 eyes developed cicatricial disease following treatment, five of these have ectopic maculae and dragging of the disc, six progressed to total retinal detachment. Two of the six eyes had stage 4a disease at the time of treatment, four had vitreoretinal surgery with one retina reattaching after surgery (Table 1).

The visual outcome is summarised in Table 2. Of the 13 eyes with normal posterior poles, 10 in children all born since January 1990 have central steady maintained fixation. Two eyes in children over 1 year of age have 6/6 forced choice preferential (FCP) and one, in a child age 5 years, has 6/12 FCP. Of the five eyes with dragged disc and macula, four in children less than 18 months old have central, unsteady, unmaintained fixation. One aged 3 years has 6/24 FCP. In addition to cicatricial disease three

Table 1 Severity of ROP and retinal outcome

Patient no	Stage of ROP	Clock hours	Zone of ROP	Retinal outcome
1	3	5	2	Cryoscars
2	3	6	2	Cryoscars
	3	8	2	Cryoscars
3	3	8	2	Cryoscars
	3	8	2	Cryoscars
4	3	12	2	Dragged disc and macula
5	3	8	2	Cryoscars
	3	8	2	Cryoscars
6	3	12	2	Total RD
	3	12	2	Dragged disc and macula
7	3	10	2	Cryoscars
	3	8	2	Cryoscars
8	3	12	2	Cryoscars
	3	6	2	Cryoscars
9	3	12	2	Total RD
10	4			Total RD
	4			Total RD
11	3	5	2	Total RD
	3	8	2	Dragged disc and macula
12	3	12	2	Cryoscars
13	3	8	2	Cryoscars
14	3	8	2	Cryoscars
15	3	10	2	Dragged disc and macula
16	3	8	2	Dragged disc and macula

Table 2 Retinal outcome and visual acuity

Visual acuity	Age	Retinal outcome	Number
CSM	<1 year	Normal posterior pole	10
6/6 FCP	>1 year	Normal posterior pole	2
6/12 FCP	5 years	Normal posterior pole	1
CUSUM	<18 months	Dragged disc and macula	4
6/24 Sn	3 years	Dragged disc and macula	1
NPL	<2 years	Total RD	6

of these children have optic nerve hypoplasia. One child has severe hydrocephalus and cerebral atrophy following grade IV intraventricular haemorrhage which makes even basic visual assessment very difficult.

In the 13 eyes with normal disc and macula three have hypermetropia, one has astigmatism, five have myopia of −1·0 DS and two have myopia of −7·0 DS. In four eyes with cicatricial disease all have myopia ranging from −1·5 DS to −8·0 DS. Refraction was not possible in the remaining eyes due to retinal detachment.

One child with initial successful uncomplicated cryotherapy developed a retrolental membrane and total retinal detachment 2 months following cryosurgery. Two eyes developed retinal haemorrhage near the ridge which spontaneously resolved. One other child had severe chemosis which resolved spontaneously after 3 days. Cryopexy was applied under general anaesthesia in 14 infants and apart from assisted ventilation for 24 hours in two infants, no other major anaesthetic problems were encountered.

Discussion
The current theory for the development of ROP is the release of a vasoproliferative factor from the anterior avascular retina which stimulates neovascularisation.[2] Cryotherapy to the ischaemic retina, which is thought to reduce the formation of this vasoproliferative factor,[13] is presently the only effective treatment in established ROP. Therefore effective screening and proper staging are essential. In our unit we screen all infants under 1500 g and under 30 weeks of gestation. We perform the first examination at 6 weeks using the indirect ophthalmoscope and eye speculum. The pupil is widely dilated using 0·5% cyclopentolate and 2·5% phenylephrine.

While we have in the main adopted the CRYOROP criteria treating stage 3 threshold disease, we have treated both eyes in some children and stage 4 in one child. We have used gestational age only in this prospective study. Others[14] have highlighted the concept of postmenstrual or postconceptual age which is calculated as the sum of the gestational age at birth plus the postnatal age at which retinopathy is discovered. They raised the interesting concept that the age at which ROP is first seen is controlled by the stage of retinal development rather than neonatal events.

The CRYOROP group defined a structural unfavourable outcome as (1) a retinal fold involving the macula, and (2) total retinal detachment. In comparing our results 13 eyes have normal posterior poles and 11 have an unfavourable outcome. Five have dragging of the disc and macula, including one eye which had successful retinal repair, and six have total retinal detachment. Our results show that the retinal outcome is better with treatment at early stage 3 threshold rather than late stage 3 or stage 4 (Table 1). Others have also advocated cryotherapy at an earlier stage and have reported good results.[5] Not all eyes with subthreshold disease escape visual disability[16] but the problem

we face is that 90% of children with stage 2 regress spontaneously and cryotherapy is a destructive form of treatment with short and long-term complications.

We realise the inaccuracy of our crude visual estimations; however fixation patterns in young infants have been shown to correlate with final visual outcome.[17] It is also important to emphasise that these visions have not been matched with age norms and this will be the subject of a longer follow-up study. Despite these limitations our results highlight a better visual outcome in eyes with normal posterior poles and a poorer outcome in eyes with cicatricial disease, although some maintain at least navigational vision.

The effect of cryotherapy on the final refractive error also needs to be determined by long-term follow-up. It has been suggested that cryotherapy may increase myopia.[18] In this study the eyes with normal posterior poles have refractive errors which range across the board with high myopia in only one child. Those with cicatrical disease, where it was possible to measure refraction, all have myopia. While our numbers are too small to determine statistical significance perhaps it is reasonable to propose that it is the end point of the disease rather than cryotherapy which determines eye growth and the ultimate refractive error.

We applied cryotherapy under general anaesthesia in contrast to the CRYOROP group where general anaesthesia was used in only 27% of cases. We are better able to apply cryopexy in this environment and our anaesthetist and neonatologist is happier with this approach. Apart from chemosis and retinal haemorrhage which spontaneously resolved, the most severe complication was the development of a retrolental membrane and total retinal detachment 2 months following successful cryoapplication in one eye. This eye showed regression of ROP 2 weeks post treatment. This possibly may have been due to the cryotherapy itself rather than progression of ROP. The CRYOROP trial reported ocular complications such as conjunctival haematoma and laceration, retinal, preretinal, and vitreous haemorrhage. Systemic complications in the same group included bradycardia, arrhythmias, and significant apnoea. Brown[19] reported a series with respiratory and cardiorespiratory arrest. In our study cryopexy was applied under general anaesthesia in 14 infants, requiring assisted ventilation in two infants only.

Recently indirect laser therapy to the avascular retina has been advocated as an alternative to cryotherapy.[20] Its advantages include greater control over the degree of ablative therapy required. However it involves an expensive outlay for a new laser system. Cryotherapy is inexpensive, more mobile, widely available, and relatively easy to apply. In our view it will remain the treatment of choice in most centres for the foreseeable future.

In summary cryotherapy works and is presently the most effective weapon in our fight against blindness in ROP. We feel this study is important as it includes not only children with normal posterior poles but also children with cicatricial disease who have maintained

navigational vision or better, after cryopexy, who might otherwise have gone blind. The present concept of threshold disease as the cut-off point for treatment of ROP was determined by consensus rather than by scientific data. We feel this criterion may need to be reviewed.

1 Phelps DL. Retinopathy of prematurity: an estimation of vision loss in the United States – 1979. *Pediatrics* 1981; **67**: 924–6.
2 Goggin M, O'Keefe M. Childhood blindness in the Rep of Ireland – a national survey. *Br J Ophthalmol* 1991; **75**: 425–9.
3 Payne JW, Patz A. Treatment of acute proliferative retrolental fibroplasia. *Trans Am Acad Ophthalmol Otolaryngol* 1972; **76**: 1234–41.
4 Yamashita Y. Studies on retinopathy of prematurity. III. Cryocautery for retinopathy of prematurity. *Jap J Clin Ophthalmol* 1972; **26**: 385–93.
5 Kingham JD. Acute retrolental fibroplasia. Treatment by cryosurgery. *Arch Ophthalmol* 1978; **96**; 2049–53.
6 Hindle NW, Leyton J. Prevention of cicatricial retrolental fibroplasia by cryotherapy. *Can J Ophthalmol* 1978; **13**: 277–82.
7 Ben-Sira I, Nissenkorn I, Grunwald E, Yassur Y. Treatment of acute retrolental fibroplasia by cryopexy. *Br J Ophthalmol* 1980; **64**: 758–62.
8 Keith CG. Visual outcome and effect of treatment in Stage III developing retrolental fibroplasia. *Br J Ophthalmol* 1982; **62**: 446–9.
9 Tasman W. Management of retinopathy of prematurity. *Ophthalmology* 1985; **92**: 995–9.

10 Hindle NW. Cryotherapy for retinopathy of prematurity: timing of intervention. *Br J Ophthalmol* 1986; **70**: 269–76.
11 Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Arch Ophthalmol* 1988; **106**: 471–9.
12 Taylor CM, Weiss JB, Kissum RD, Garner A. Effect of O2 tensions on the quantities of procollagenase activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; **70**: 162–5.
13 Diabetic Retinopathy Research Group. Preliminary report on the effects of photocoagulation therapy. *Am J Ophthalmol* 1976; **81**: 383–96.
14 Fielder AR, Ng YK, Levene MI. Retinopathy of prematurity: age of onset. *Arch Dis Child* 1986; **61**: 774–8.
15 Nissenkorn I, Ben-Sira I, Kremer I, Gaton DD, Krikler R, Weilunsky E, Merlob P. Eleven years' experience with retinopathy of prematurity: visual results and contribution of cryoablation. *Br J Ophthalmol* 1991; **75**: 158–9.
16 Hindle NW. Cryotherapy for retinopathy of prematurity, none, one or both eyes. [Letter.] *Arch Ophthalmol* 1990; **108**: 1375.
17 Costenbader F, Blair DR, McPhail A. Vision in strabismus. *Arch Ophthalmol* 1948; **40**: 438–53.
18 Cryotherapy for Retinopathy of Prematurity Cooperative group. Multicenter trial of cryotherapy for retinopathy of prematurity: one-year outcome – structure and function. *Arch Ophthalmol* 1990; **108**: 1408–16.
19 Brown CG, Tasman WS, Naidoff M, Schaffer DB, Quinn G, Bhutani VK. Systemic complications associated with retinal cryoablation for retinopathy of prematurity. *Ophthalmology* 1990; **97**: 855–8.
20 McNamara JA, Tasman W, Brown GC, Federman JL. Laser photocoagulation for stage 3+ retinopathy of prematurity. *Ophthalmology* 1991; **98**: 576–80.