Effect of partial cryoablation on retinopathy of prematurity

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Abstract

Cryotherapy has been shown to be an effective treatment for retinopathy of prematurity stage 3. It is said to reduce the unfavourable outcome of the disease by 50%. The accepted method of therapy includes ablation of the whole avascular retina from the ridge to the ora serrata. This is achieved by two to three rows of cryoapplications. When 360° cryo treatment is performed, it requires 52 cryo applications. We present our method of cryotherapy which involves only one row of cryoapplications in the avascular retina anterior to the fibrovascular ridge. An average of 25-30 cryoapplications was required for a 360° treatment. The anatomical results in 23 babies are presented. Complete regression of active retinopathy was found in all.

The first reports¹⁻³ of the use of cryotherapy in the control of the proliferative phases of retinopathy of prematurity (ROP) varied in their conclusions regarding the advantages and limitations of this form of treatment.

In 1978 Kingham⁴ published his disappointing clinical results following cryotherapy. In the same year Hindle and Leyton⁵ reported their successful clinicopathological results in the treatment of active ROP by cryotherapy. Their methods of treatment was similar to that used in the previous reports¹⁻⁴ and consisted of direct freezing of the ridge and the adjacent areas anterior and posterior to it by one to two circular rows of cryoapplications.⁵ Hindle and Leyton showed that in most of the treated eyes the ridge disappeared and no cicatrization developed. Keith, using the same direct method of cryoablation of the ridge but not the avascular retina anterior to it, found no beneficial effect.⁶

In contrast to that method of treatment¹⁻⁶ Ben-Sira and colleagues⁷ described an indirect treatment scheme involving cryoablation of the whole avascular retina, while avoiding direct treatment of the ridge and the neovascular growths posterior to it.⁷ Nissenkorn and coworkers reported a clinicopathological case which showed almost complete regression of the disease in the areas posterior to the atrophic chorioretinal cryo scars and low-grade active disease between the scars.⁸ Subsequently additional reports presented encouraging results following the use of the latter indirect method of cryo treatment.⁹⁻¹²

The encouraging preliminary results of the multicentre trial of cryotherapy for retinopathy of prematurity were published in 1988.¹² The method of cryotherapy described included ablation of the whole avascular retina, from the ridge to the ora serrata, while avoiding the ridge itself. It was found that cryotherapy conferred an

approximately 50% reduction in the unfavourable outcome of ROP.¹²

During the last three years we observed that cryotherapy involving ablation only of the avascular retina close to the ridge, by one row of cryoapplications, without reaching the ora serrata, leads to regression of the neovascular growths. We present here the results of this mode of partial cryotherapy performed in the premature babies under our care in the last three years.

Patients and methods

The charts of all premature babies undergoing cryotherapy due to ROP stage 3 from January 1986 to December 1988 were reviewed. All babies had a birth weight of less than 1250 g and gestational age of less than 28 weeks, except for one neonate whose gestational age was 32 weeks (Table 1). These 23 infants were found to have ROP stage 3 (moderate). The treatment was performed in zone I in six infants (12 eyes) and in zone II in 17 infants (32 eyes). The cryoablation was performed differently from our previous treatment protocol, which we applied until 1986.⁷

The cryotherapy was done with a standard retinal probe. One row of contiguous applications were applied to the avascular retina, reaching the anterior edge of the ridge. The rest of the anteriorly located avascular retina was left untreated. The end point of each application was whitening of the retina. A freezing time of 3 to 4 seconds was usually needed to produce the necessary cryo effect in the retina. Treatment of

Table 1 Patients' clinical data

Case	Treated eye	GA (weeks)	BW (g)	Zone of ROP		Extent of ROP		Cryoablation (hours)	
				RE	LE	RE	LE	RE	LE
1	BE	28	690	II	II	12	12	12	12
2	BE	26	790	I	I	12	12	12	12
3	BE	25	680	I	I	12	12	12	12
4	BE	28	670	I	I	12	12	12	12
5	BE	26	700	II	II	8	8	8	8
6	BE	27	750	II	II	7	7	7	7
7	BE	26	680	I	I	12	12	12	12
8	BE	26	670	I	I	12	12	12	12
9	BE	28	700	II	II	6	6	6	6
10	BE	26	770	II	II	6	6	6	6
11	LE	26	870	II	II	-	6	-	6
12	LE	27	900	II	II	-	6	-	6
13	BE	26	870	II	II	6	6	6	6
14	LE	28	750	II	II	-	8	-	8
15	BE	24	720	I	I	12	12	12	12
16	BE	28	580	II	II	6	6	6	6
17	BE	25	860	II	II	6	6	6	6
18	BE	26	810	II	II	6	6	6	6
19	LE	32	900	II	II	-	6	-	6
20	BE	26	930	II	II	6	6	6	6
21	BE	27	950	II	II	12	12	12	12
22	BE	28	950	II	II	6	6	6	6
23	BE	27	1120	II	II	6	6	6	6

GA = gestational age. BW = birth weight.

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Figure 1 Schematic drawing of partial cryoablation treatment of ROP stage 3, zone II.

the entire circumference of the retina required an average of approximately 25–30 separate treatment spots (Fig 1). In most cases no conjunctival incision was required except for the very small premature babies in whom ROP was located in zone I.

Most of the babies underwent the treatment with topical anaesthetic drops (oxybuprocaine 0.4%), while a neonatologist was in attendance. Six of the neonates who had vasoproliferative disease in zone I (cases 2, 3, 4, 7, 8, 15, Table 1) were treated under general anaesthesia. In those patients a conjunctival incision 3–4 mm in length was made in each quadrant, a cataract cryoprobe was inserted, and one row of cryoapplications was applied throughout 360° in zone I. Post-operatively, 1 drop of atropine 0.5% and dexamethasone 1% were instilled three times a day for one week.

The infants underwent weekly examinations in the first month after treatment, followed by monthly examinations in the following three months, and once every six months thereafter. All infants underwent orthoptic evaluation and retinoscopy until 1 year of age.

Results

In most of the infants the disease was found to be symmetrical, and both eyes were treated with cryoablation (Table 1). The cryotherapy was performed at an average age of 6–12 weeks. In six infants with zone I disease the cryoablation was performed in both eyes throughout the whole retinal circumference (12 clock hours) (Table 1). Thirteen infants with bilateral zone II disease received cryotherapy extending from 6 to 12 clock hours in both eyes (Table 1). Four infants with asymmetrical disease had cryoablation performed in zone II in one eye only, for 6 clock hours (Table 1).

One week after cryoablation the dilatation and tortuosity of posterior pole vessels decreased, and two to four weeks later the active retinal and extraretinal vasoproliferations disappeared in the majority of the cases. In three cases with zone I disease where the cryoapplication did not reach the anterior edge of the ridge we had to add a few cryoapplications closer to the ridge, after which the regression occurred. The results of the two-year follow-up after cryotherapy based on fundus examination revealed total regression of

the active vasoproliferative disease. Atrophic pigmented chorioretinal scars were found anterior to the equator in 70% of the babies and posterior to the equator in 30%. No child developed retinal detachment.

The results of orthoptic evaluation, refraction, and visual acuity testing will be reported in the future.

Discussion

Animal studies have shown that the developing retinal vasculature responds in a biphasic way: (a) initial vasoconstriction and vaso-obliteration in the presence of raised arterial oxygen levels, and (b), on return to room air, by peripheral retinal ischaemia with consequent neovascular proliferation, possibly due to secretion of a vasoproliferative substance by the ischaemic retina.^{13–15} Taylor *et al.*¹⁶ have shown that a vasoproliferative factor is released under these conditions. In 1984 Kretzer *et al.*¹⁷ described a theory for the induction of ROP according to which a high level of oxygen may trigger extensive gap junction formation between the spindle cells of the avascular vanguard retina, located close to the rearguard zone. Therefore it may be assumed that the development of ROP is triggered by a vasoproliferative substance produced in the ischaemic vanguard retina, as happens in other ischaemic retinopathies.^{18,19} The greater the stimulus in the area of the ischaemic retina to produce this substance, the greater the vasoproliferation, as for example in zone I retinopathy or Rush type ROP.²⁰ As in other ischaemic retinopathies, destruction of the ischaemic tissue is believed to reduce the formation of this vasoproliferative factor and to arrest the vasoproliferative disease.^{21,22} The main question confronting us since we started to perform cryotherapy in active stage 3 ROP is how much avascular retina should be ablated. Between 1976 and 1983 we have been cryoablating the whole avascular retina, avoiding the ridge itself and the neovascular growths, according to a protocol which was described by Ben-Sira *et al.*^{7,23} Since 1986 we have changed the method of cryoablation by which the cryoapplications were performed only anterior to the ridge on the avascular retina, in one row. The rationale for this partial cryotherapy was that the main stimulus for neovascularisation is probably located in the avascular retina adjacent to the ridge, where the metabolic activity of the spindle cells is highest and where one can also find increased numbers of gap junctions.¹⁷ This method has proved to be successful in conferring regression of the neovascular proliferations posterior to the ridge, in all the above presented premature babies. No serious postoperative complications such as rhegmatogenous retinal detachment were noted.²⁴

Therefore we are of the opinion that the treatment, to begin with, in a baby with ROP stage 3 should be partial cryoablation consisting of one or a maximum of two rows of cryoapplications in the avascular retina close to the ridge. The treatment must be done in a confluent pattern close to the ridge, and one must avoid gaps between the cryoablation spots (Fig 1).

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