Original articles

Retinopathy of prematurity: incidence and treatment

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SUMMARY   The incidence of retinopathy of prematurity in infants with a birthweight ≤2500 g admitted to a tertiary neonatal intensive care unit between 1977 and 1983 was 20% of all survivors. There was a reciprocal relation between birthweight and the incidence of the disease, with an incidence of 68% in infants weighing ≤1000 g at birth. Cryotherapy of the avascular retina was performed if the acute disease progressed rapidly during stage 3 and the amount of fibrovascular proliferation was mild to moderate with signs of plus disease (presence of appreciable posterior pole vascular tortuosity and dilatation and the presence of engorgement of iris vessels). This method of treatment was performed in 4% of all survivors: in 26% of infants weighing ≤1000 g at birth and 5% of infants weighing 1001–1500 g. No infants had cicatricial disease greater than stage 2 on follow-up. The absence of any severe cicatricial disease or blindness in this large group of high risk infants suggests that when indicated and performed on the avascular retina cryotherapy may be an important method of treatment.

Retinopathy of prematurity has not been eliminated, as previously predicted, since the establishment of neonatal intensive care units in the late 1960s.[1-3] Phelps estimates that 30% of infants with a birthweight of 1000 g or less will develop cicatricial disease with 8% becoming blind, and 2·2% of infants with a birthweight between 1001 and 1500 g will have cicatricial disease with 0·5% becoming blind.[4]

As retinopathy of prematurity appears to be a multifactorial disease[5] its prevention, even with the most accurate methods of monitoring blood gases, is probably impossible. The use of vitamin E might help to prevent the more severe forms of the disease in infants with a gestational age of 28 weeks or more.[6] In younger infants, however, severe disease of the eyes is still common. Cryotherapy or photocoagulation has been performed on infants who have developed the more severe form of the active disease, with conflicting results.[7-15]

In 1975 a tertiary neonatal intensive care unit was opened at the Beilinson Medical Centre. An ophthalmologist started to examine all infants admitted routinely, and, according to our protocol, cryotherapy was performed in the more severe cases of acute retinopathy. We report our experience over a seven year period.

Patients and methods

All infants admitted to the neonatal intensive care unit underwent routine eye examinations by a senior ophthalmologist trained to recognise all stages of active and cicatricial retinopathy. The first eye examination was performed between 3 and 4 weeks of age after the infants' condition had stabilised and they no longer required assisted ventilation. The eye examinations were repeated weekly or more often, depending on the existence, progression, or arrest of the disease. Retinopathy was graded initially according to Patz's classification.[16] A new classification has been suggested by an international group of ophthalmologists,[17] and the staging of the acute disease has been changed accordingly.

From 1 January 1977 to 31 December 1983 1340 infants with a birthweight of ≤2500 g (inborn and outborn) were admitted to the intensive care unit, 1070 (80%) survived (Table 1). Of the infants admitted, 667 had a birthweight of ≤1500 g and 70% survived. Infants were grouped according to their birthweight only because of difficulties in verifying gestational age, especially in very small infants.

Cryotherapy was performed, as described previously,[12] when the progression of the disease during stage 3 was rapid and the amount of

Table 1 *Survival and incidence of acute retinopathy of prematurity in relation to birthweight*

	Birthweight (g)						Total
	≤750	751–1000	1001–1250	1251–1500	1501–2000	2001–2500	≤2500
No of admissions	60	147	217	243	481	192	1340
No of survivors (%)	9 (15)	78 (53)	165 (76)	212 (87)	439 (91)	167 (87)	1070 (80)
No with acute retinopathy (%)	3 (33)	56 (72)	58 (35)	45 (21)	46 (10)	3 (2)	211 (20)

fibrovascular proliferation was mild to moderate. These findings were accompanied by signs of plus disease (presence of appreciable posterior pole vascular tortuosity and dilatation and engorgement of iris vessels).[17] Informed written consent was obtained from parents before the infants were treated.

Infants with a birthweight of ≤1800 g and all ventilated infants were seen at a neonatal follow up clinic for neurological and developmental evaluation and ophthalmologic examination within one month of discharge from the unit, or earlier if active retinopathy was present. Subsequently, the infants were seen at regular intervals. Infants with a birthweight of ≤1500 g were followed up to the age of 8 years. The rate of attrition was low (2–3%).

Results

Acute retinopathy of prematurity was diagnosed in 211 (20%) of the surviving infants (Table 1). In infants with a birthweight of between 751 g and 1000 g the incidence of acute retinopathy of prematurity was 72%; it decreased to 35% in infants weighing between 1001 g and 1250 g and to 21% in those weighing between 1251 g and 1500 g. The incidence was still fairly high in infants weighing between 1501 g and 2000 g (10%) but was only 2% in those between 2001 g and 2500 g. Of the infants with acute retinopathy, 105 (50%) had retinopathy stage 1; 58 (28%) had stage 2, and 48 (22%) stage 3 (Table 2).

Cryotherapy was usually performed on both eyes, but if only one eye required treatment the better eye was not initially treated. Of the infants weighing ≤1000 g, 26% of the survivors were treated (Table 3); of those weighing 1001–1500 g, 5% were treated; and of those between 1501 g and 2000 g, only 0·5% were treated. Cryotherapy was performed in 21% of all infants with acute retinopathy and in 4% of all surviving infants with a birthweight of ≤2500 g. On follow up 37 (18%) of these infants had cicatricial

Table 2 *Stage of acute retinopathy of prematurity in relation to birthweight*

Acute retinopathy Stage	Presence of:	Birthweight (g)				Total
		501–1000	1001–1250	1251–1500	1501–2500	≤2500
1	Demarcation line	20	29	22	34	105
2	Ridge	17	12	17	12	58
3	Ridge with extraretinal fibrovascular proliferation	22	17	6	3	48
4	Retinal detachment	0	0	0	0	0
	Total	59	58	45	49	211

Table 3 *Acute retinopathy of prematurity and cryotherapy in relation to birthweight*

	Birthweight (g)			Total
	≤1000	1001–1500	1501–2500	≤2500
No of survivors	87	377	606	1070
No with acute retinopathy	59	103	49	211
No treated with cryotherapy	23	19	3	45
% of acute retinopathy	39	18	6	21
% of survivors	26	5	0·5	4

Table 4 *Acute retinopathy and cicatricial disease on follow up in relation to birthweight on follow up*

	Birthweight (g)			Total
	≤1000	1001–1500	1501–2500	≤2500
No with acute retinopathy	59	103	49	211
No with stage 1 cicatricial disease (and % of acute retinopathy)	12 (20)	18 (18)	7 (14)	37 (18)
No with stage 2 cicatricial disease (and % of acute retinopathy)	7 (12)	5 (5)	2 (4)	14 (7)
No with > stage 2 cicatricial disease	0	0	0	0

disease stage 1 (Table 4) and 7% had stage 2. No infant had greater than stage 2 cicatricial disease and none were blind.

Discussion

The incidence of acute retinopathy of prematurity in our study was high, in accord with results from other studies.[2 3 6 18] There was an inverse relation between birthweight and the incidence and severity of retinopathy. The absence of severe cicatricial disease in such a large group of high risk infants was an interesting finding in this study. The survival rates of the infants admitted to the unit were similar to rates reported in other series.[19] Ventilated infants were managed and blood gases measured according to standard recommendations reported previously.[20] Vitamin E was not used routinely. It is unlikely, therefore, that the management of these sick babies had any influence on the lack of severe cicatricial disease.

The use of cryotherapy is controversial. Nagata first applied photocoagulation in the treatment of severe retinopathy of prematurity,[7] and subsequently it has been used widely in Japan.[8 9] Cryotherapy has also been used in several other centres,[10–15] and results have varied; some have reported failures or deleterious results of treatment,[11] some have reported little or no influence on the progress of the retinopathy,[10 14] while others have reported improvement or complete regression.[8 9 12 13 15]

As different classifications of the disease are used it is not always possible to compare results. The timing and method of treatment has also varied. In some centres cryotherapy has been performed only at a late stage of development of the disease, and the rate of success has been low or the condition has worsened. In most studies treatment has been performed on the demarcation line and neovascular ridge.

We treated our patients after the disease had advanced to acute stage 3 retinopathy, according to definite criteria. Cryotherapy was applied only to the avascular retina. Cryotherapy was performed in 4% of our surviving population and in 9% of infants with a birthweight of 1500 g or less (26% of infants with acute retinopathy). After treatment the eyes were examined routinely at least weekly.

Infants with a birthweight of 1800 g or less and the larger ventilated infants were followed in a special follow up clinic. Thirty seven (18%) of 211 infants with acute retinopathy have cicatricial disease stage 1 and 14 (7%) stage 2. None of the infants were blind or had serious visual impairment (cicatricial disease > stage 2). By the estimation of Phelps the expected incidence of blindness in our population was at least eight infants with more than twice that having severe cicatricial disease. Infants admitted to our unit in 1975 and 1976 were not included in this study as routine ophthalmological examinations were not performed as often as after 1976. Cryotherapy was used, however, when indicated, and no infant given cryotherapy has become blind or has serious visual impairment. As no other factor in the treatment of these infants explains the lack of any severe disease of the eyes in this large group of high risk infants our method of treatment seems to prevent severe cicatricial disease.

Hittner *et al* suggested a possible mechanism to support the treatment of the avascular retina only.[21] The pathogenesis of retinopathy was thought to be due to vasoconstriction with destruction of the endothelium of the posterior retinal vessels. The avascular peripheral retina was considered to be a quiescent region of the developing retina. Evidence suggests that embryonic spindle cells in the peripheral retina are the initial target of the disease with an increase in the extent of the gap junctions between these cells.[22] This cellular alteration removes the embryonic precursors from the normal pattern of retinal vascular development as early as 4 days after birth and triggers the severe retinopathy observed as soon as 8 weeks after birth. Hittner *et al* postulate that cryotherapy of only the avascular retina with its activated stacked spindle cells results in retinal quiescence. In contrast, cryodestruction of

the proliferating vessels with overlying haemorrhage results in further haemorrhage, neovascularisation, exudation, traction, and ultimate retinal detachment because the activated spindle cell inducer remains operational.

We, and others, noted a high incidence of retinopathy, particularly in infants with a birthweight of ≤1250 g. We suggest that careful examination of the eyes of all low birthweight infants admitted to a neonatal intensive care unit be performed within the first few weeks of life. Subsequently, regular examinations would be necessary until the retinal vessels reached the temporal ora serrata. In infants with acute retinopathy stage 1 or 2 no treatment is indicated as in 75–80% there is spontaneous regression. In 75% of infants with retinopathy stage 3, however, the disease progresses to stage 4, and the visual outcome is poor.[21] Thus when retinopathy progresses to acute stage 3 and if there are more than two hours of confluent fibrovascular proliferation cryotherapy of the avascular zone' is indicated. Using this protocol we found that no infant developed severe cicatricial disease or blindness.

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