

RESULTS OF THE TREATMENT OF ZONE I VERSUS ZONE II RETINOPATHY OF PREMATUREITY

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Abstract

Zone I retinopathy of prematurity (ROP) generally has a poorer prognosis than zone II ROP. The aim of this study was to evaluate the effect of early ROP treatment on the pathological findings on the retina at 6 months of age in relation to the extent of disorder. Preterm infants weighing less than 1500 g at birth were examined before 4 weeks of age. A total of 139 eyes in 93 infants were identified to have avascular retina. Of them, 56 eyes (39 infants) had zone I ROP (group I) and 83 (54 infants) had zone II ROP (group II). Therapy included transpupillary indirect diode-laser photocoagulation and/or trans-scleral cryotherapy. At 6 months of follow-up, the structural outcomes of treatment were assessed according to the Cryotherapy for Retinopathy Criteria and were compared between the groups. In Group I, 19 (33%) eyes had an unfavourable structural outcome while, in group II, it was 11 (13.2%) eyes ($P = 0.027$). The mean birth weight and gestational age were similar in both groups, but the mean gestational age at treatment was significantly different (32.1 ± 3.4 weeks in group I vs. 36.5 ± 3.7 weeks in group II, $P = 0.013$). It is concluded that a higher amount of unfavourable anatomic results in zone I ROP may indicate a poorer prognosis for useful vision in these infants. Special attention should be paid to atypical fundus changes in zone I ROP in order to begin treatment as early as possible.

Key words

Zone I and II retinopathy of prematurity, Diode-laser photocoagulation, Structural outcome

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retinal vasculature in preterm infants. ROP is a major cause of visual morbidity in childhood. Ablation of avascular peripheral retina, initially performed with xenon arc photocoagulation, then cryotherapy and, more recently, diode laser photocoagulation, has been shown to reduce the cicatricial sequelae of this disease.

The role of cryotherapy in treatment of infants with threshold retinopathy of prematurity has been evaluated in a multicentre study, in which parameters have been set for the effectiveness of peripheral retinal treatment (1). Indirect laser treatment has become the method of choice in zone I ROP because it has achieved good results (2,3). However, these are still not as satisfactory as the outcomes achieved by the same method in infants with zone II ROP. The cause of zone

I ROP is not fully understood yet and it has been suggested that a new classification is needed to define the appropriate timing for intervention, as the retinal morphology of zone I disease does not always agree with that defined by the International Classification of Retinopathy of Prematurity (ICROP) (4). We analysed two groups of eyes, one with zone I and the other with zone II ROP, treated by both cryotherapy and photocoagulation, in order to assess their clinical characteristics and treatment outcomes.

MATERIALS AND METHODS

PATIENTS

All preterm infants (birth weight less than 1500 g) born in the obstetric departments of the Faculty of Medicine in Brno between January 1996 and December 2000 were screened for ROP. According to the regular screening programme for ROP, 642 premature newborns were examined. Of these, 139 eyes in 93 infants developed threshold ROP in zone I (Group I, 56 eyes) or zone II (Group II, 83 eyes). All these patients were referred to our department and their avascular retinas was treated by cryotherapy and/or diode laser photocoagulation.

EXAMINATION AND CLASSIFICATION OF ROP

The infants were first examined for ROP within 4 weeks of birth by an experienced ophthalmologist. Dilating drops (Mydracyl, Neo-Synephrin) were administered 30 min before examination performed with an indirect ophthalmoscope (Nidek, Japan), using a lid speculum and a scleral depressor for ocular rotation and peripheral indentation. This approach allowed us to get a stereoscopic, wide-angle view of the retina.

The stage and location of ROP was recorded according to the International Classification of ROP (ICROP). Stage 1 is characterised by a demarcation line between the normal retina close to the optic nerve and nonvascularised retina at the periphery. Stage 2 ROP has a ridge of scar tissue and new vessels in place of the demarcation line. Stage 3 ROP shows an increased size of the vascular ridge, with growth of fibrovascular tissue on the ridge that extends out into the vitreous. Stage 4 refers to a partial retinal detachment. In Stage 4A, the detachment does not include the macula. In Stage 4B, the macula is detached and the visual potential is markedly decreased. Stage 5 ROP implies a complete retinal detachment, with no useful vision. The threshold ROP 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, as in the standard protocol of the Cryotherapy for Retinopathy of Prematurity Study (CRPS).

We classified each patient as having either zone I or zone II disease. Zone I ROP was defined as threshold ROP present in the circular area around the optic disc with a twice the disc to fovea distance; zone II ROP was defined as threshold ROP in the retinal area, concentric to Zone I, extending up to the nasal ora serrata. Special attention was given to morphological atypical signs not included in the ICROP. A structural outcome was classified as unfavourable when a fold through the macula, or partial retinal detachment including the macula (stage 4B) or total retinal detachment (stage 5) was present. These criteria were defined by the CRYO-ROP Cooperative Group.

TREATMENT METHOD

Cryotherapy was performed trans-sclerally by a cryoprobe (Erbe, Germany). Multiple applications of cryotherapy were done in order to treat the entire avascular area anterior to the neovascular ridge. Each application involved freezing until an ice ball forms was created on the retinal surface.

Photocoagulation involved the use of an indirect diode laser (Nidek DC 3300, Japan) in its continuous mode at a wavelength of 810 nm. Photocoagulation was applied transpupillary to the

entire avascular retina for 100–200 ms at an energy of 200–600 mW. For each eye, the energy was adjusted to produce graywhite burnt spots. It was delivered through a +20 diopter lens with the aid of a lid speculum and scleral depressor. The spots produced in the avascular retina followed a tight scatter pattern with a half to one burn width between two neighbouring burns. The treatment was performed under topical anaesthesia and sedation in an operating room. The patients were checked every week until neovascularisation regressed and then followed up for a minimum of 6 months.

The criteria for treatment of threshold zone I ROP were re-evaluated for the eyes in which plus disease was also present. The standard treatment for zone I disease was used in eyes that had a progressive dilation and tortuosity of posterior pole vessels found on two consecutive examinations, with concurrent evidence of neovascular proliferation, either as a ridge or flat network of vessels. The retinal detachment of the posterior pole or macular fold or retrolental fibroplasia obscuring the view of the posterior pole were regarded as signs of a poor treatment outcome (1).

STATISTICAL ANALYSIS

Proportions of the eyes with poor structural outcomes were assessed and compared between group I and group II; the results were statistically analysed by Student's *t* test and *P* values of less than 0.05 were considered to be significant.

RESULTS

Of 93 infants (139 eyes) diagnosed as having retinopathy of prematurity in this study, 56 eyes (group I) had zone I ROP and 83 eyes (group II) had zone II ROP. In group I infants, the mean birthweight was 875 ± 319 g (range, 565 to 1280) at the mean gestational age 25.8 ± 2.8 weeks (range, 24 to 31); for group II these values were 983 ± 428 g (range, 630 to 1580) and 27.4 ± 3.6 weeks (range, 25 to 34). Group I required treatment at a mean gestational age of 32.1 ± 3.4 weeks (range, 31 to 37) and group II at 36.5 ± 3.7 weeks (range, 31.2 to 40.5). This difference was statistically significant ($P = 0.013$).

The energy level needed to obtain a desirable burn ranged between 200 and 600 mW. In general, a posterior part of the avascular retina near the ridge needed more energy for an effective burn; a high energy level was required more often in group I than group II. The number of spots used ranged from 850 to 2435 (average, 1675) per eye for group I and from 450 to 1680 spots (average, 943) for group II.

At 6 months, 19 eyes of group I (33% of 56 eyes) and 11 of group II (13.2% of 83 eyes) had unfavourable structural outcomes ($P = 0.027$; *Fig. 1*). In group I, 10 eyes had a total retinal detachment, five eyes had a partial retinal detachment involving the macula and four had a macular fold. In group II, three eyes had a macular fold, five had a partial retinal detachment involving the macula and three had a total retinal detachment. Some eyes with zone I ROP showed morphology that was not typical and therefore difficult to assess according to the ICROP criteria.

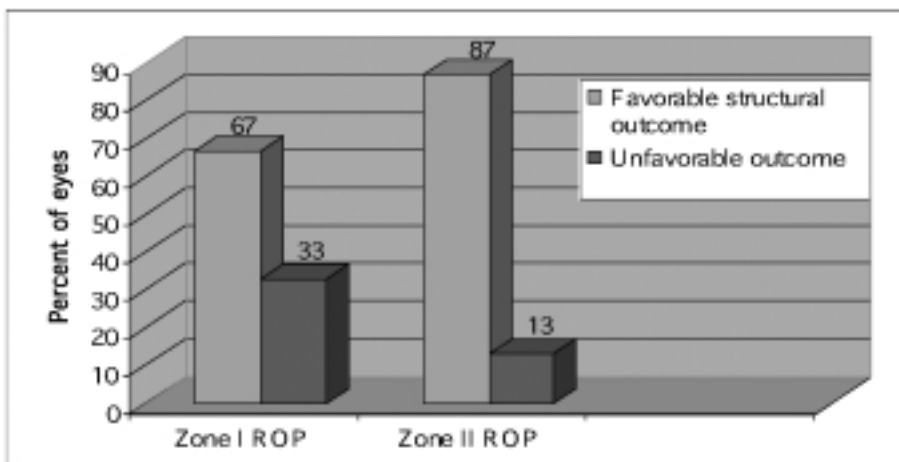


Fig 1

Treatment outcomes in terms of retinal morphology in infants with retinopathy of prematurity (ROP). Zone I ROP group included 56 eyes in 39 infants, and zone II ROP group comprised 83 eyes in 54 infants.

DISCUSSION

ROP is a potentially vision-devastating disease that can often be treated successfully if it is diagnosed in time. Fortunately, in most patients with ROP, abnormal retinal vessels disappear or regress spontaneously. If the vessels continue to proliferate, which involves a risk of retinal detachment and visual loss, treatment of the avascular retina in the threshold stage of retinopathy is indicated and is carried out by cryotherapy or photocoagulation.

In infants with retinopathy of prematurity, zone I disease is much less common than zone II ROP. Several studies have reported that zone I ROP is the reason for treatment in only 1% to 9% of the total number of treated patients (1,5,6). In the eyes with zone I ROP and in agreement with the literature data, we observed a high degree of symmetry between the two eyes (7), which is not always the case of zone II ROP patients.

Since there was no significant difference in the mean weight and gestational age at birth between groups I and II, it was not possible to estimate at birth which infants were at a greater risk of developing zone I or zone II ROP.

In exceptional cases we treated zone I ROP eyes, with an extent of less than 5 clock hours and stage 3, when plus disease was observed to be progressing. In many group I eyes, we found on the first examination that ROP progressed beyond the extent of 5 clock hours of stage 3 and plus disease had developed. This

may explain a faster course that, together with atypical morphology, was observed in zone I eyes. The difference in age at treatment in our study may be explained by the fact that zone I disease either developed earlier or progressed faster than zone II ROP; in some cases the involvement of both these factors was considered. These facts have been much discussed in the relevant literature (3, 5, 6, 7, 8, 9) and, therefore, we recommend that very premature infants should be screened at a chronological age of 4 weeks even if the first examination may only involve investigation of the posterior retina. In the CRYO-ROP study (1), the threshold ROP was not found in infants before age 5 weeks whereas, in our study, the threshold stage indicated for treatment by the CRYO-ROP criteria were found on average at age 7.1 weeks.

The first findings are very important because they determine the whole course of ROP treatment. The cryotherapy study shows that an early intervention has markedly reduced the visual disorder due to retinopathy as compared with the eyes treated late or untreated. In zone I ROP eyes, the rate of unfavourable outcomes was reduced by only 17% (92% unfavourable outcome in untreated control eyes vs 75% unfavourable outcome in treated eyes), as compared to an average reduction by 39.5% in all eyes with ROP (1).

Much better results have been reported with laser treatment (3,9). *Fleming et al.* (10) reported a 100% success rate (0% unfavorable outcome); however, they treated zone I ROP much earlier than the standard definition of threshold would dictate. *Capone et al.* (2) reported a 17% unfavourable outcome rate. *Shapiro et al.* (11) reported a 36% unfavourable outcome rate in zone I eyes that were treated after extraretinal proliferation had developed. In their study, the amount of proliferation at treatment was variable depending on the age at which the infant was referred for treatment. *Vander et al.* (7) reported a 16% unfavourable outcome rate in zone I eyes treated before the threshold ROP developed and an 18% unfavourable outcome rate for control eyes treated at the threshold stage.

In zone I ROP eyes, our results at 6-month follow-up showed a 33% unfavourable outcome rate while zone II ROP infants had only a 13% unfavourable outcome rate. This implies that a new definition of the threshold stage for zone I ROP will be necessary. This will require a better understanding of the development of zone I disease. Not only is the rate of progression different between zone I and zone II disease, but the characteristic stepwise progression from stage 1 to 3 in zone I may not occur (2,11). We confirmed that, at least in some of zone I eyes, shunting does not occur across the ridge, as characteristic of stage II, but it occurs in the peripheral arteriovenous arcade, as described by *Shapiro* (11). When proliferation ensues, it arises from the arteriovenous arcades in flat nets that become thicker and more elevated with time, forming a brush-like neovascular network. Characteristic stage 2 may be absent and stage 1 may quickly progress to a network of neovascularisation that may extend for several

clock hours. In our study, atypical morphology made it difficult to stage zone I eyes by using the ICROP criteria. In some cases, a demarcation vessel was seen in place of the demarcation line between vascular and avascular retina characteristic of stage 1 ROP, together with severe dilatation and tortuosity of adjacent retinal vessels.

Further studies focused on identification of characteristic features of zone I ROP in its development are needed in order to find more exact criteria defining the threshold retinopathy of prematurity and thus permitting more effective treatment.

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SROVNÁNÍ VÝSLEDKŮ LÉČBY RETINOPATIE NEDONOŠENÝCH V ZÓNĚ I A V ZÓNĚ II

S o u h r n

Děti s retinopatií nedonošených (ROP) začínající v zóně I v oblasti zadního polu oka mají horší zrakovou prognózu než je tomu u dětí s ROP v zóně II. Autoři zhodnotili klinické znaky a výsledky léčby dětí s ROP zóny I ve srovnání se skupinou dětí s ROP zóny II. Předčasně narozené děti s porodní hmotností menší než 1500g byly vyšetřeny ve věku do 4 týdnů po porodu. Klinické nálezy byly hodnoceny podle mezinárodní klasifikace ROP (ICROP). U všech dětí v souboru byl přesně identifikován počátek ROP v zóně I, II. Prahové stadium ROP bylo definováno podle mezinárodního standardu Cryotherapy for Retinopathy of Prematurity Study (CRPS). K destrukci avaskulární sítnice byla použita transpupilární indirektní fotokoagulace diodovým laserem anebo transsklerální kryoterapie. Za 6 měsíců sledování po léčbě byly zhodnoceny strukturální anatomické výsledky podle kritérií CRPS. Byly analyzovány rozdíly ve výsledcích léčby očí s ROP začínající v zóně I nebo v zóně II. Ve skupině I bylo 56 očí (39 dětí) s ROP v zóně I. Ve skupině II bylo 83 očí (54 dětí) s ROP v zóně II. Za 6 měsíců po léčbě 33% dětí s ROP v zóně I a 13,2% dětí s ROP v zóně II mělo nepříznivý strukturální nález na zadním segmentu ($P = 0.027$). Průměrná porodní hmotnost a gestační věk byly podobné v obou skupinách, ale průměrný gestační věk v době operačního zákroku byl signifikantně rozdílný (32.1 ± 3.4 týdne u případů ROP v zóně I a 36.5 ± 3.7 týdne u případů ROP v zóně II, $P = 0.013$). Z toho vyplývá, že více nepříznivých anatomických výsledků v případě ROP začínající v zóně I odráží méně příznivou prognózu vývoje užitečného vidění u těchto novorozenců. Zvláštní pozornost musí být věnována atypickým změnám na očním pozadí přítomným u ROP v zóně I, aby léčba mohla být zahájena včas.

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