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The Outcome of Cryotherapy for Retinopathy of Prematurity (ROP) According to ROP Location

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Cryotherapy has been shown to be an effective treatment for retinopathy of prematurity (ROP) stage 3+. However, the outcome of cryotherapy is less favorable in zone 1 ROP than in zone 2 ROP. We suspected whether there may be differences in the outcomes of cryotherapy if the zone of ROP is further divided. So we reviewed the records of 85 premature infants (145 eyes) who had undergone cryotherapy for ROP. The frequencies of favorable outcome were 42.9% of 14 eyes (zone 1), 78.9% of 38 eyes (posterior zone 2), 92.9% of 70 eyes (mid zone 2), and 100.0% of 23 eyes (anterior zone 2) , respectively ($p < 0.001$). These results suggest that the more posteriorly the ROP is located, the less favorable the outcome of cryotherapy.

Key words: cryotherapy, favorable outcome, location, retinopathy of prematurity, zone

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of blindness among the children, most likely due to the increased survival of extremely small babies in modern neonatal intensive care units.[1-4]

During the past decades, cryotherapy has been commonly used for the treatment of the acute stages of ROP and has been shown to be an effective treatment for ROP stage 3+.[5-9] The multicenter trial of cryotherapy for retinopathy of prematurity (Cryo-ROP Study) proved that cryotherapy reduced the risk of unfavorable ocular outcome from threshold ROP.[10-13] However, eyes with zone 1 disease had a higher percentage of unfavorable outcomes compared to the eyes with zone 2 disease after cryotherapy. Thus, the treatment mostly benefited eyes with zone 2 disease.

These reports[10-13] of poorer outcome of cryotherapy in eyes with zone 1 ROP than in eyes with zone 2 ROP lead us to believe that there may be a locational difference in the outcome of cryotherapy for ROP. The purpose of this study was to ascertain whether there was a difference in the anatomical outcome of cryotherapy according to the locations of ROP when the area of zone 2 is further divided into three subzones.

PATIENTS AND METHODS

The medical records of 85 premature infants who had undergone cryotherapy for ROP from November, 1987 to September, 1993 and had been followed for more than over 2 months postoperatively at our hospital, were reviewed retrospectively.

Ocular examination of premature infants had been performed in the nursery area using a lid

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speculum, scleral depressor and binocular indirect ophthalmoscope. The International Classification of ROP[14,15] had been used in the description of the acute stages of ROP. But we had described the location of zone 2 in further detail. When ROP was located near the boundary of zone 1 and 2 but not considered to be in zone 1 with careful examination, the location was classified as posterior zone 2. When there was uncertainty as to the appropriate zone between zone 2 and 3, the location was described as anterior zone 2. When the location of ROP was easily defined as zone 2 with indirect ophthalmoscopic examination, the location was described as mid zone 2.

Indications for cryotherapy had been based on the criteria defined by the CRYO-ROP study10-that is stage 3+ threshold disease (5 or more contiguous or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2, in the presence of plus disease). However, we had differed from the CRYO-ROP study10 in that we had treated both eyes in infants with bilateral threshold disease. After April, 1991, in addition to the threshold ROP, our indication for cryotherapy included a prethreshold posterior zone ROP (ROP in zone 1 or in the posterior zone 2) with associated plus disease.

The cryotherapy was performed in the operating room under the general anesthesia according to the CRYO-ROP study protocol and the entire avascular retina anterior to the ridge had been treated.

After cryotherapy the infants were examined with hand held slit lamp and indirect ophthalmoscope once a week until regression or progression could be documented and then examined monthly.

anatomical outcome of cryotherapy was assessed with a funduscopic appearance in the last examination according to the CRYO-ROP study.[10] Outcomes were classified as unfavorable if the funduscopy revealed; (1) a posterior retinal fold involving the macula; (2) a retinal detachment involving zone 1 of the posterior pole or (3) retrolental tissue or mass that obscure the view of the posterior pole (cicatricial ROP grade III-V, Reese classification16). All eyes with other fundus appearances, such as normal posterior pole or macular dragging, etc. (cicatricial ROP grade O-II, Reese classification) were classified as having a favorable outcome.

We further divided the area of zone 2 into three subzones; posterior, mid, and anterior zone 2 according to our more detailed descriptions about zone 2 during the examination of premature infants. According to these further divided locations of acute stage of ROP, we divided eyes of 85 premature infants into four groups as follows: zone 1 group, posterior zone 2 group, mid zone 2 group, and anterior zone 2 group, and investigated the anatomical outcomes of cryotherapy in each group.

RESULTS

Cryotherapy was performed on 150 eyes of 88 premature infants. Among them 3 infants had not been followed up over 2 months after cryotherapy, and 145 eyes of 85 premature infants were analyzed for the results in this study. The birth weight of the infants ranged from 800 g to 2,700 g (mean 1386 g, standard deviation 325.0 g) and gestational age

Table 1. Structural outcome of cryotherapy

	Location of ROP (zone)	Favorable			Unfavorable	Total No.
		Gr 0-I	Gr II	Total(%)	Gr III-V(%)	of eyes(%)
Threshold stage	1	3	1	4 (44.4)	5 (55.6)	9 (100.0)
	post. 2	18	7	25 (80.6)	6 (19.4)	31 (100.0)
	mid 2	57	8	65 (92.9)	5 (7.1)	70 (100.0)
	ant. 2	22	1	23 (100.0)	0 (0.0)	23 (100.0)
Prethreshold stage	1	2	0	2 (40.0)	3 (60.0)	5 (100.0)
	post. 2	4	1	5 (71.4)	2 (28.6)	7 (100.0)
Total		106	18	124 (85.5)	21 (14.5)	145 (100.0)

Gr O-V; cicatricial ROP grade according to the Reese classification[16]

Table 2. Structural outcome of cryotherapy according to the location of ROP

Location of ROP (zone)	Favorable outcome	Unfavorable outcome	Total No. of eyes
1	6 (42.9%)	8 (57.1%)	14 (9.6%)
post. 2*	30 (78.9%)	8 (21.1%)	38 (26.2%)
mid 2*	65 (92.9%)	5 (7.1%)	70 (48.3%)
ant. 2*	23 (100.0%)	0 (0.0%)	23 (15.9%)
Total	124 (85.5%)	21 (14.5%)	145 (100.0%)

$\chi^2_{MH} = 24.295$, $p < 0.000$, Mantel-Haenszel χ^2 test,
**: $\chi^2_{MH} = 7.940$, $p < 0.005$, Mantel-Haenszel χ^2 test*

ranged from 25 weeks to 36 weeks (mean 30.3 weeks, standard deviation 2.36 weeks). They ranged in chronological age from 4-16 weeks and in postconceptional age from 33-48 weeks at the time of treatment, and were followed up for mean periods of 23.9 months (range from 2-72 months) following cryotherapy.

The overall percentage of favorable outcomes in 145 eyes was 85.5% (124 eyes) (Table 1). When 145 eyes were divided into four groups, 14 eyes belonged to the zone 1 group, 38 eyes to the posterior zone 2 group, 70 eyes to the mid zone 2 group, and 23 eyes to the anterior zone 2 group. Percentages of favorable outcome of cryotherapy were 42.9% in the zone 1 group, 78.9% in the posterior zone 2 group, 92.9% in the mid zone 2 group, and 100.0% in the anterior zone 2 group (Table 2). A significant trend is the higher frequency of a favorable outcome in the group of eyes with the more anteriorly located ROP ($\chi^2_{MH} = 24.295$, $p < 0.000$, Mantel-Haenszel χ^2 test).

Even within only the zone 2 group, there is a significant increasing trend of frequency of a favorable outcome as ROP becomes more anteriorly located ($\chi^2_{MH} = 7.94$, $p < 0.005$, Mantel-Haenszel χ^2 test).

Postoperative ocular and/or systemic complications are shown in Table 3.

Table 3. Complications after cryotherapy (145 eyes of 85 patients)

complication	No. (%) of cases
retinal or preretinal hemorrhage	7 (4.8)
vitreous hemorrhage	3 (2.1)
choroidal rupture	1 (0.7)
pseudo-pterygium	3 (2.1)
pneumonia	1 (1.2)
postoperative apnea*	12 (14.1)

**: postoperative apnea which needed a ventilator care over 24 hours.*

DISCUSSION

On the classification of the acute stages of ROP, accurate definement of zone is clinically very difficult as the anatomic landmarks, other than the disc and ora, may be hard to discern in the premature eye. Indeed, anatomic landmarks needed to identify the equator are sufficiently varied in humans, thus rendering precise locations difficult at any age.[14] The international classification of retinopathy of prematurity (ICROP)[14] recognized this problem and recommended that when there was uncertainty as to the appropriate zone to locate the disease, it should be located in the more posterior zone. Therefore, our classification about the location of ROP may be inaccurate and not consistent in every case, but we attempted to define accurately the location of ROP with careful attention. We believe that the posterior zone 2 in our study may correspond to the posterior one-fourth of zone 2, the mid zone 2 to the middle two-fourth of zone 2, and the anterior zone 2 to the anterior one-fourth of zone 2.

The infants treated in this study were relatively large, with a mean birth weight of 1,386 g, and were relatively mature, with a mean gestational age of 30.3 weeks when compared with the CRYO-ROP study.[10-12]

The current theory for the development of ROP is the release of a vasoproliferative factor from the

anterior avascular retina which stimulates neovascularization.[4,17] Animal studies have shown that the developing retinal vasculature was initially vasoconstricted and vaso-obliterated in the presence of raised arterial oxygen levels and on return to room air, peripheral retinal ischemia with consequent neovascular proliferation developed, possibly due to secretion of a vasoproliferative substance by the ischemic retina.[18-20] Destruction of the ischemic retina is believed to reduce the formation of this vasoproliferative factor and to arrest the vasoproliferative disease.[21]

In addition to the poorer outcome of cryotherapy for zone 1 ROP in comparison with zone 2 ROP, we observed that in eyes with zone 2 ROP, outcome of cryotherapy for posteriorly located ROP was poorer than for anteriorly located ROP (Table 2). We speculate that this may be due to the fact that the larger the area of avascular retina that is affected, the greater the stimulus for the vasoproliferation and the more, it is more difficult to perform complete cryoablation of whole avascular retina.

The anatomocal outcome of cryotherapy for posterior zone 2 was not as favorable as that of mid and anterior zone 2 (Table 1, 2). These results suggest that the most of unfavorable outcomes of cryotherapy in zone 2 ROP may be due to being located in posterior zone 2. The multicenter trial of cryotherapy for retinopathy of prematurity reported 26.1% and 27.4% of incidence of unfavorable outcome of cryotherapy in zone 2 ROP after 3-month and 1-year follow-up examination, respectively.[11,12] It is possible that these results of unfavorable outcomes in zone 2 ROP may mainly be due to the posterior zone 2 ROP, however, there has been no comment about more specific locations within zone 2 in the previous reports.[11,12]

We as well as others[11,12] observed the poor outcome of cryotherapy for posteriorly located ROP. Some advocated cryotherapy at an earlier stage and reported good results.[12,22] Therefore, we performed cryotherapy at an earlier stage (prethreshold stage) in these posteriorly located ROP (zone 1 and posterior zone 2 ROP) in an attempt to improve the outcome of cryotherapy. The results of cryotherapy for posteriorly located ROP showed no difference between early cryotherapy at the prethreshold stage and late cryotherapy at the threshold stage (Table 1). However, we do not have sufficient data to make conclusions about early cryotherapy in posteriorly located ROP. Further cases are needed to accumulate data before efficacy of early cryotherapy is to be determined. From our experience, our opinion is that for treatment of posterior zone ROP, earlier treatment by cryotherapy with or without preventive scleral encircling or other treatment modalities such as laser photocoagulation should be tried in order to prevent retinal detachment and blindness.

In conclusion, we have shown that there is a difference in the anatomical outcome of cryotherapy for ROP even in the three subzones of zone 2, thus, there may be a locational difference in the anatomical outcome of cryotherapy for ROP. We suggest that for the posterior zone ROP, earlier and more aggressive treatments should be tried.

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