

Original

## Retinopathy of Prematurity: Screening, Incidence and Risk Factors Analysis

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### Key Words

birth body weight;  
cryotherapy;  
gestational age;  
laser indirect ophthalmoscopy;  
retinopathy of prematurity

**Background.** The sequela of retinopathy of prematurity (ROP) is an important cause of infant blindness. This study was designed to screen the high-risk premature infants and investigate the incidence and risk factors associated with the development of ROP.

**Methods.** From October 1997 to October 1998, all premature infants with birth body weight (BBW) less than 2000 gm or gestational age (GA) less than 36 weeks were enrolled and underwent ophthalmologic examination at 4 to 6 weeks of age at Taipei Veterans General Hospital. The perinatal variables were analyzed to evaluate their correlation with the development of ROP.

**Results.** In total 108 premature infants, the incidence for development of ROP was 25% (27 in 108 patients). The threshold ROP occurred in 15 eyes (7%). The average BBW and GA ( $1267 \pm 341$  gm and  $29.7 \pm 2.7$  weeks) were significantly lower in ROP group than in the non-ROP group ( $1703 \pm 368$  gm and  $32.3 \pm 2.2$  weeks). The artificial ventilation for more than 5 days, chronic lung disease and periventricular leukomalacia were significant risk factors associated with highest rate of ROP. The respiratory distress syndrome, intraventricular hemorrhage, congenital heart disease and sepsis were significant risk factors accompanied by moderate rate of ROP.

**Conclusion.** Low birth body weight and young gestational age are the most important risk factors in the development of ROP. The analysis of risk factors will be helpful in understanding and prediction of ROP formation in high-risk neonates. The timely clinical screening retinal examination of high-risk premature infants is important to prevent the development of advanced ROP. [*Chin Med J (Taipei) 2001;64:706-712*]

The retinopathy of prematurity (ROP) is characterized by abnormal vascular development of retina in premature infants, which is one of the major causes of infant blindness. Its incidence increases with the improvement in neonatal survival in very low body weight premature infants. However, there were few

studies on the incidence and risk factors of this important morbidity of premature neonates in Taiwan.<sup>1</sup>

High concentration of oxygen therapy was previously thought as the major factor in the development of ROP. However, some reports have found ROP in cases without oxygen therapy.<sup>2</sup> Even after oxygen

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therapy, not all premature infants develop ROP. These evidences suggested that risk factors other than oxygen might play an important role in the development of ROP.

We conducted this retrospective study to screen the high-risk premature neonates, with the main purpose to investigate the incidence of ROP and to determine the possible risk factors associated with the development of ROP.

## Methods

There were totally 108 premature infants enrolled in this study from Oct. 1997 to Oct. 1998. The inclusion criteria were infants who were, either less than 36 weeks of gestational age or less than 2000 gm of birth body weight, in the neonatal newborn room or intensive care unit at Taipei Veterans General Hospital.

The ophthalmic examination was initially performed to screen the high-risk premature infants at postnatal age of 4 to 6 weeks under indirect ophthalmoscopy. The stage and severity of ROP was classified according to the international classification of ROP (ICROP, Table 1).<sup>3</sup> The follow-up retinal examination was performed every one or two weeks till ROP regression, complete vasculogenesis of retina or

the development of threshold ROP was observed. All threshold ROP cases were treated with cryotherapy or diode laser therapy using laser indirect ophthalmoscopy. The threshold severity of ROP was defined as five or more contiguous or eight cumulative 30 sectors (clock hours) of stage 3 plus ROP in zone 1 or 2. The plus sign represented the dilatation and tortuosity of the retinal blood vessels in the posterior pole.

The perinatal variables (clinical data and pediatric illness) were recorded from the pediatric chart for each case, including the birth body weight, gestational age, sex, birth place, duration of artificial ventilation with either mechanic ventilator (IMV) or continuous positive airway pressure (CPAP) more than 5 days, respiratory distress syndrome (RDS), chronic lung disease (CLD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), congenital heart disease (CHD), sepsis, hyperbilirubinemia and multiple birth etc.. Each variable was analyzed to evaluate its correlation with the development of ROP.

Statistical analysis was performed with a computerized program. Significance was tested with the chi-square test with Yates' correction and Fisher's exact test. The Odds ratio for each possible risk factor was also calculated.

## Results

Totally 108 premature infants underwent the screening retinal examination for ROP. The gestational age ranged from 24 to 37 weeks (mean  $31.6 \pm 2.6$  weeks); the birth body weight ranged from 620 to 2870 gm (mean  $1594 \pm 407$  gm). There were 60 boys (55.6%) and 48 girls. The majority of patients were born at Taipei Veterans General Hospital (N = 96, 88.9%), and 12 (10.1%) patients were transferred

**Table 1. The international classification of retinopathy of prematurity**

Stage	Characteristics
1	Demarcation line
2	Ridge
3	Ridge with extraretinal fibrovascular proliferation
4	Subtotal retinal detachment: (A) Extrafoveal (B) Retinal detachment including fovea
5	Total retinal detachment

**Table 2. The comparison of the mean birth body weight and gestational age between the ROP and non-ROP group**

	ROP group (N = 27)	Non-ROP group (N = 81)	p value
Mean birth body weight (gm)	$1267 \pm 341$	$1703 \pm 368$	< 0.001
Mean gestational age (wk)	$29.7 \pm 2.7$	$32.3 \pm 2.2$	< 0.001

**Table 3. The correlation between the positive rate of ROP screening and the distribution of birth body weight in premature infants**

Birth body weight (gm)	No. of cases	No. (%) of ROP
≤ 1000	8	7 (87.5)
1000-1200	12	5 (41.7)
1200-1400	14	4 (28.6)
1400-1600	26	7 (26.9)
1600-2000	30	3 (10.0)
> 2000	18	1 (5.6)

**Table 4. The correlation between the positive rate of ROP screening and the distribution of gestational age in premature infants**

Gestational age (wk)	No. of cases	No. (%) of ROP
≤ 28	14	7 (50.0)
28-32	52	16 (30.8)
32-34	28	4 (14.3)
> 34	14	0 (0)

**Table 5. The correlation between the stages of ROP and the birth body weight, gestational age in premature infants**

Stages of ROP	Birth body weight (gm)	Gestational age (wk)
0 (n = 163)	1702 ± 366	32.3 ± 2.2
1 (n = 24)	1390 ± 340	30.8 ± 2.2
2 (n = 15)	1204 ± 197	29.9 ± 1.4
3 (n = 12)	1190 ± 365	28.0 ± 3.6
4 (n = 2)	620 ± 0	25.0 ± 0

Data are expressed as mean ± SD.

**Table 6. The risk factors analysis of retinopathy of prematurity**

Risk factors	ROP group eyes (N=27)	Non-ROP group eyes (N=81)	p value	Odds ratio
O <sub>2</sub> usage > 5 days	16	12	0.001	8.36
RDS	23	49	0.018	3.76
CLD	6	1	0.001	22.86
IVH	5	3	0.012	5.83
PVL	5	1	0.001	18.18
CHD	5	4	0.027	4.38
Sepsis	9	12	0.035	2.88
Hyperbilirubin	5	30	0.075	0.39
Multiple birth	13	43	0.657	0.82

RDS = respiratory distress syndrome; CLD = chronic lung disease; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; CHD = congenital heart disease.

from other hospitals. There was multiple birth in 56 (51.9%), and single birth in 52 cases (48.1%).

The prevalence of ROP development was 25% (27 in 108 patients). The threshold ROP (stage 3 plus and above) occurred in 15 eyes (7%). Table 2 shows statistically significant difference in lower body weight and younger gestational age between ROP group and non-ROP group ( $p < 0.001$ ).

The correlation between the positive rate of ROP screening and the distribution of birth body weight or gestational age is shown in Tables 3 and 4 respectively. Lower birth body weight or younger gestational age tended to associate with the higher rate of ROP development.

The correlation between the staging of ROP and the distribution of birth body weight or gestational age is shown in Table 5. High severity of ROP tended to associate with lower birth body weight and younger gestational age.

There were 13 multiple births and 14 single births among the 27 ROP cases. The likelihood of ROP development seemed to be similar between multiple and single birth patients.

The perinatal variables were tested to evaluate their correlation with the development of ROP (Table 6). The artificial ventilation for more than 5 days, chronic lung disease, and periventricular leukomalacia were significant risk factors associated with highest rate of ROP ( $p = 0.001$ ). Respiratory distress syndrome, intraventricular hemorrhage, congenital heart disease and sepsis were sig-

nificant risk factors accompanied by moderate rate of ROP ( $0.01 < p < 0.05$ ). Multiple birth and hyperbilirubinemia were not the significant risk factors of ROP development.

## Discussion

The importance of the clinical screening examination of the fundus of high-risk premature infants has been confirmed because of the improved clinical outcome in infants with acute, active ROP after either cryotherapy<sup>4-5</sup> or transpupillary laser treatment.<sup>6-7</sup> However, the optimal timing of initial screening retinal examination of ROP at nursery is still controversial. The earlier screening protocol would result in many unnecessary examinations, while later screening protocol might fail to diagnose the onset of threshold ROP and miss the golden time of therapy. According to Palmer's report,<sup>8</sup> the 7<sup>th</sup> to 9<sup>th</sup> week after birth is the best time for yielding the largest number of ROP cases. Recently, the American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology released a joint statement recommending that the initial screening examination should be performed between the 4 and 6 weeks of chronological age, or 31 and 33 weeks of postconceptional age.<sup>9</sup> In our study, the screening protocol was performed between 4 and 6 weeks after birth. In the early course study of CRYO-ROP cooperative group,<sup>10</sup> the timing of retinal vascular events of ROP correlated more closely with the postconceptional age than the chronological age. They observed that 95% of stage 2 ROP have the onset at 32 weeks or later. The threshold ROP (stage 3) was reached at a mean of 36.9 weeks, in range of 33.6 to 42.0 weeks. Therefore, most authors agree that the initial screening performed at 4 to 6 weeks after birth is appropriate and safe for the detection of acute ROP.

The incidence of ROP varied according to the screening time and protocol. The incidence of ROP in the current study was 25%, which was higher than

most reports in United States.<sup>11</sup> Our inclusion criteria of screening was different from other centers. We examined all premature infants with body weight less than 2000 gm or gestational age less than 36 weeks. As our hospital is a referral center, many premature babies with very low body weight were transferred from other hospitals. The above two reasons lead to the higher incidence of ROP in our study. The incidence of threshold ROP (7%) in our study was similar to other reports in literature.<sup>11</sup>

The pathogenesis of the development of ROP is still uncertain. Patz et al,<sup>12</sup> in a prospective controlled trial, clearly demonstrated the causal effect of high oxygen administration on the development of ROP. However, the oxygen therapy is no longer the only and most important factor of the development of ROP. Recent observation has found ROP to be a disease of multifactorial origin, of which oxygen therapy is but one factor.<sup>13,14</sup> The individual susceptibility of premature infants and many other factors may involve in the development of ROP. Additional risk factors include low birth weight, younger gestational age, hypercarbia, acidosis, vitamin E deficiency, intracranial hemorrhage and multiple blood transfusion.<sup>15</sup> In the current study, the ROP group had statistically significant lower birth weight and younger gestational age than the BBW and GA in the non-ROP group. The incidence and severity of ROP in the current study were also higher in lower birth weight and young gestational age categories. We concluded that the birth body weight and gestational age are the most important risk factors in the development of ROP, and are also the best indicators of immaturity in premature infants. In the current study, the multiple birth itself is not a risk factor of ROP development, coexistence of low body weight and gestational age is even more important.<sup>16</sup>

In our study, the artificial ventilation for more than 5 days is a statistically significant risk factor in the development of ROP. The duration of ventilation is usually associated with a longer time of high concentration of oxygen therapy. During the normal embryonic development, the retinal vessels begin to

grow outward from the optic disc in the 4<sup>th</sup> month, and do not reach the ora serrata until nearly full term. The retina of premature newborn is therefore in completely vascularized with a peripheral avascular zone. In the retina of ROP infants, normal retinal blood vessel development arrests, and vaso-obliteration of some pre-existing retinal vessels occurs. It has been suggested that the relative hyperoxia of extrauterine environment under high concentration of oxygen therapy causes the suppression of normal vessel development and vaso-obliteration.<sup>17</sup> In an animal model of oxygen-induced retinopathy, an association between exposure to hyperoxia and vaso-obliteration has been observed.<sup>18</sup> The ischemic retina subsequently produces angiogenic factors, in which vascular endothelial growth factor plays a major role to result in retinal neovascularization for maturation in ROP.<sup>19</sup>

Several other risk factors were clearly found to correlate with the development of ROP in the current study. Respiratory distress syndrome and chronic lung disease were known to associate with systemic hypoxia, which will lead to retina ischemia. The etiology of periventricular leukomalacia comes from hypoxia and blood hypoperfusion of cerebrum which eventually has similar influence on the retina ischemia. Sepsis in the low body weight premature infants is frequently accompanied with hypotension which will impair tissue perfusion with local hypoxia to render retina under the risk of ROP development.

In conclusion, the analysis of risk factors of the development of ROP will help understand and predict ROP for maturation in high-risk neonates. Since ROP may produce serious sequela of infant blindness, effort must be made to prevent the development of advanced ROP. Timely screening eye examination of high risk premature infants is very important.

## References

1. Chou YH, Teng RJ, Yau KIT, Yang CM. Retinopathy of prematurity: an analysis of risk factors. *J Formos Med Assoc* 1993;92:440-5.
2. Lucey JF, Dangman B. A reexamination of the role of oxygen in retrolental fibroplasia. *Pediatrics* 1984;73:82-96.
3. Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130-34.
4. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: preliminary results. *Arch Ophthalmol* 1988;106:471-9.
5. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: three-month outcome. *Arch Ophthalmol* 1990;108:195-204.
6. Hunter DG, Repka MX. Diode laser photocoagulation for threshold retinopathy of prematurity: a randomized study. *Ophthalmology* 1993;100:238-44.
7. Laser ROP Study Group. Laser therapy for retinopathy of prematurity. *Arch Ophthalmol* 1994;112:154-6.
8. Palmer EA. Optimal timing of examination for acute retrolental fibroplasia. *Ophthalmology* 1981;88:662-8.
9. American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. *Ophthalmology* 1997;104:888-9.
10. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, Tung B. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991;98:1628-40.
11. Reischer SH, Amir I, Shohant M, Krikler R, Nissenkorn I, Sira IB. Retinopathy of prematurity: incidence and treatment. *Arch Dis Child* 1985;60:698-701.
12. Patz A, Hoeck LE, De La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia: i, nursery observations. *Am J Ophthalmol* 1952;35:1248-53.
13. Flynn JT. Retinopathy of prematurity. *Pediatr Clin North Am* 1987;34:1487-516.
14. Kinsey VE, Arnold HJ, Kalina RE, Stern L, Stahlman M, Odell G, et al. PaO<sub>2</sub> level and retrolental fibroplasia. *Pediatrics* 1977;60:655-68.
15. Sira IB, Nissenkorn I, Kremer I. Retinopathy of Prematurity. *Surv Ophthalmol* 1998;33:1-16.
16. Blumenfeld LC, Siatkowski RM, Johnson RA, Feuer WJ, Flynn JT. Retinopathy of prematurity in multiple-gestation pregnancies. *Am J Ophthalmol* 1998;125:197-203.
17. Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol* 1954;38:397-

- 432.
18. Smith LE, Wesolowski E, McLellan A, Kostyk SK, D'Amato R, Sullivan R, D'Amore PA. Oxygen-induced retinopathy in the mouse. *Invest Ophthalmol Vis Sci* 1994; 1994;35:101-11.
19. Pierce EA, Foley ED, Smith LEH. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. *Arch Ophthalmol* 1996;114:1219-28.