DURATION OF OXYGEN THERAPY AND EXCHANGE TRANSFUSION AS RISK FACTORS ASSOCIATED WITH RETINOPATHY OF PREMATURITY IN VERY LOW BIRTHWEIGHT INFANTS

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SUMMARY

One hundred and thirteen consecutive infants with a very low birthweight of less than 1500 g were followed prospectively for 6 months to determine the incidence of retinopathy of prematurity (ROP) and associated risk factors. Of this group, 36 (31.9%) infants developed ROP (13 infants had stage 1 ROP, nine had stage 2, six had stage 3, six had stage 4, and two had cicatricial stage ROP). Stepwise logistic regression analysis of various potential risk factors (birthweight, gestation, duration of oxygen therapy, duration of ventilation, highest documented PaO_2 and exchange transfusion) showed that only two risk factors were significantly associated with the development of ROP. These risk factors were: the duration of oxygen therapy ($p = 0.0005$) and exchange transfusion during the neonatal period (odds ratio 5.754, 95% confidence interval 1.002 to 32.997, $p = 0.049$). The equation of the regression model is: log (odds of developing ROP) = $-0.8395 + 0.1447$ (OXY) $- 0.8750$ (ET), where OXY is the duration of oxygen therapy in days, ET = -1 when there was a history of exchange transfusion, and ET = 1 when there was no history of exchange transfusion.

Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy which occurs primarily but not exclusively in preterm babies with immature retinal vasculature.[1] Numerous risk factors occurring during the neonatal period have been implicated as being associated with the occurrence of this condition. These include gestation less than 32 weeks, very low birthweight (VLBW) (<1500 g), use of supplemental oxygen, apnoea requiring face mask and bag ventilation, duration of ventilation, repeated blood transfusions, prolonged parenteral nutrition, hypoxaemia, hypercarbia, hypocarbia, intraventricular haemorrhage, sepsis and retinal illumination.[1–19] A genetic basis for this condition has also been suggested recently.[20]

The incidence of ROP in VLBW infants in Western countries has been reported to vary between 34.9% and 60.1%.[21–23] The incidence of this condition has not been well studied amongst Asian babies. In a survey of babies in the Midlands of the United Kingdom, the incidence of ROP was thought to be higher amongst Oriental babies[23], but no detailed study has been performed on babies born in Asia.

The objectives of this study were to determine the incidence of ROP in a group of VLBW Malaysian infants and the risk factors associated with this condition.

PATIENTS AND METHODS

A prospective, observational cohort study was carried out on consecutive VLBW infants (<1500 g) born in Kuala Lumpur Maternity Hospital between 1 December 1989 and 31 December 1992 and admitted to the neonatal intensive care unit (NICU) of the same hospital, and who survived for at least 6 months. The gestational age was assessed by the Ballard's score.[24]

All infants admitted to the NICU were observed for development of respiratory distress syndrome (RDS). Supplemental oxygen via a head box was

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given when there was evidence of hypoxia. The inspired oxygen was supplied to maintain the infant's arterial oxygen tension (PaO_2) between 7.0 and 10.0 kPa. During this study, most neonates were not monitored with pulse oximeters because of shortage of equipment. Oxygenation status was monitored by intermittent arterial blood sampling. Endotracheal intubation and intermittent positive pressure ventilation were indicated when any of the following conditions were present: severe respiratory distress with a Silverman score of >6,[25] hypoxia with PaO_2 <7.0 kPa, hypercarbia with $PaCO_2$ >8.0 kPa, or recurrent apnoea. The infants were weaned off ventilatory support and supplemental oxygen as soon as their clinical condition and blood gases showed improvement. Surfactant therapy was not available in Malaysia during the study period. The infants were fed by intravenous drip until they were stable enough to tolerate enteral feeds. Serum bilirubin was monitored serially in patients who were clinically jaundiced. Exchange blood transfusion was carried out when the indirect serum bilirubin exceeded 280 μmol/l or when there was overwhelming septicaemia not responding to antibiotic treatment. Cranial ultrasound scanning was carried out on each infant weekly until discharge to look for periventricular and intraventricular haemorrhage. The infants were discharged from the nursery when they had attained a body weight of 1750 g with steady daily weight gain and tolerated oral feeding.

All VLBW infants who died before 6 months of age (after correction for prematurity), or who had major congenital malformations, were excluded from the study.

At 4–6 weeks after birth, when the general condition of the infant was satisfactory, an ophthalmological examination of the fundus was carried out with the use of an indirect ophthalmoscope in the NICU by one of three ophthalmologists (S.L.T., M.K.N. or M.K.A.). If the infants were discharged before that age, the eye examination was then carried out in the outpatient clinic. For the ophthalmological examination, the eyes were dilated with 0.5% cyclopentolate and 2.5% phenylephrine drops. ROP was classified according to the International Classification of Retinopathy of Prematurity.[26] The most advanced stage of ROP detected in the infant was used for analysis. Subsequent eye examinations were carried out depending on the fundal findings until there was no risk of developing severe ROP. When ROP was detected, ophthalmological examination was repeated weekly until vascularisation of the retina was completed. Cryotherapy was advocated for patients with stage 3 ROP.

A sample size of at least 81 infants was required for this study in order to detect a 30% rate of occurrence of ROP with a relative precision of ±10% at the 95% confidence level. For univariate comparison between infants with and without ROP, the chi-squared test (or Fisher's exact test if expected cell values were less than 5) was used for categorical variables and the two-sample Student's *t*-test for continuous variables. Stepwise logistic regression analysis (using the SPSS/PC statistical package) was employed to determine the significance of various potential risk factors associated with ROP. A p value of less than 0.05 was considered significant.

RESULTS

During the study period, 419 VLBW infants were born in the hospital. Thirty-seven (8.8%) infants died in the labour room within half an hour of birth and 52 (12.4%) were transferred elsewhere for intensive care treatment because of shortage of infant ventilators in the NICU. Of the remaining 330 infants admitted to the NICU, 155 (47%) died before discharge from the hospital while the remaining 175 (53%) were discharged alive. Two of the 175 survivors had Down's syndrome and were subsequently excluded from our study.

Of the remaining 173 eligible infants, 113 (65.3%) had an ophthalmological examination and were followed up for the detection of ROP during the first 6 months of life. ROP was detected in 31.9% (36/113) of these infants. Of these 36 infants, 36.1% (13/36) developed stage 1 ROP, 25% (9/36) stage 2, 16.7% (6/36) stage 3, 16.7% (6/36) stage 4 and 5.6% (2/36) advanced to the circatricial stage. Cryotherapy was not carried out on any infants with stage 3 ROP because their parents either refused treatment or absconded from follow-up.

Table I shows the relationship of basic characteristics, perinatal and postnatal factors with ROP. Univariate analysis shows that, when compared with infants who did not develop ROP, infants with ROP had significantly lower mean birthweight and mean gestational age, but significantly higher mean documented PaO_2, longer mean duration of ventilatory support and oxygen therapy, and a significantly higher incidence of exchange transfusion during the neonatal period. Interestingly, there was no significant difference between the different ethnic groups.

Stepwise logistic regression analysis of the various potential risk factors (birthweight, gestation, duration of oxygen therapy, duration of ventilation, highest documented PaO_2 and exchange transfusion) was subsequently carried out. Two risk factors were shown to be significantly associated with the development of ROP (Table II). These risk factors were: the duration of oxygen therapy and a history of exchange transfusion during the neonatal period. The risk of developing ROP was significantly higher in infants who had exchange transfusion compared

Table I. Relationship of basic characteristics, perinatal and postnatal factors with retinopathy of prematurity (ROP)

	No ROP (n = 77)	ROP (n = 36)	p value
Sex			
Male	34	17	
Female	43	19	0.918
Race			
Malay	52	24	
Others	25	12	0.901
Birthweight [(g), mean (SD)]	1279 (158)	1184 (174)	0.007
Gestation [weeks, mean (SD)]	32.1 (2.5)	30.6 (2.3)	0.008
Small-for-gestation age	43	20	1.000
Problems during pregnancy			
Pre-eclampsia	27	7	0.142
Multiple pregnancy	12	5	0.962
Placenta praevia	3	1	1.000
Chorioamnionitis	2	4	0.080
Mode of delivery			
SVD	39	23	
Others	38	13	0.265
Apgar score [mean (SD)]			
1 minute	7.1 (1.6)	6.8 (1.7)	0.342
5 minutes	8.5 (0.8)	8.1 (1.1)	0.119
Resuscitated at birth	50	21	0.080
Hypothermia	31	16	0.829
Respiratory distress syndrome	49	28	0.198
Septicaemia	29	20	0.113
Apnoea	13	8	0.674
Exchange transfusion	2	7	<0.001
Duration of ventilation [days, mean (SD)]	1.2 (2.5)	3.2 (5.2)	0.038
Duration of oxygen therapy [days, mean (SD)]	3.6 (5.2)	9.4 (7.8)	0.004
Peak $PaCO_2$ [kPa, mean (SD)]	4.64 (1.27)	5.45 (2.25)	0.112
Lowest pH [mean (SD)]	7.22 (0.28)	7.18 (0.20)	0.094
Lowest PaO_2 [kPa, mean (SD)]	11.5 (4.1)	10.9 (5.4)	0.191
Highest PaO_2 [kPa, mean (SD)]	22.6 (8.7)	26.4 (8.7)	0.046

with those who had not undergone the procedure (odds ratio 5.754, 95% confidence interval 1.002 to 32.997, $p = 0.0497$). In this study, the indications for exchange transfusion were severe unconjugated hyperbilirubinaemia ($n = 5$) and septicaemia ($n = 4$). The logistic regression analysis also showed that with every additional day of supplemental oxygen therapy during the neonatal period, the affected infant had a 1.156 times higher risk of developing ROP when compared with infants who were exposed to 1 day less of oxygen therapy (odds ratio 1.156, 95% confidence interval 1.056 to 1.254, $p = 0.0005$). During this study, the mean duration of oxygen therapy among the 36 infants with ROP was 9.4 days (Table I) and the maximum duration was 30 days. Using the results of estimated beta for the duration of oxygen therapy derived from the logistic regression analysis, we calculated the probability of our VLBW infants developing ROP following exposure to different durations of oxygen therapy (Fig. 1). The results show that as the duration of exposure to oxygen therapy increased, the risk of developing of ROP rose markedly. For example, infants exposed to 30 days of oxygen therapy had a greater than 90% chance of developing ROP. For infants who had exchange transfusion, even without exposure to oxygen therapy, the risk of developing ROP was more than 50%. When these infants were exposed to oxygen therapy in addition to exchange transfusion, the risk of developing ROP increased further.

DISCUSSION

The incidence of ROP in our study of 31.9% was somewhat lower than that of other reported studies.[21–23] However, these studies may not be comparable due to the different standards of neonatal care among the NICUs, the survival rates of VLBW infants, frequency of eye examination, the population under study (whether hospital-based or community-based) and the method of study. In this

Table II. Logistic regression analysis of significant risk factors associated with the development of retinopathy of prematurity

Variables	Estimated beta	Standard error of estimated beta	Odds ratio	95% confidence interval for odds ratios
Duration of oxygen therapy	0.1447	0.0415	1.156	1.065 to 1.254
Exchange transfusion	−0.8750	0.4458	5.754	1.002 to 32.997

The equation of the regression model is: log (odds of developing ROP) = −0.8395 + 0.1447 (OXY) −0.8750 (ET), where OXY is the duration of oxygen therapy in days, ET = −1 when there was history of exchange transfusion, and ET = 1 when there was no history of exchange transfusion.

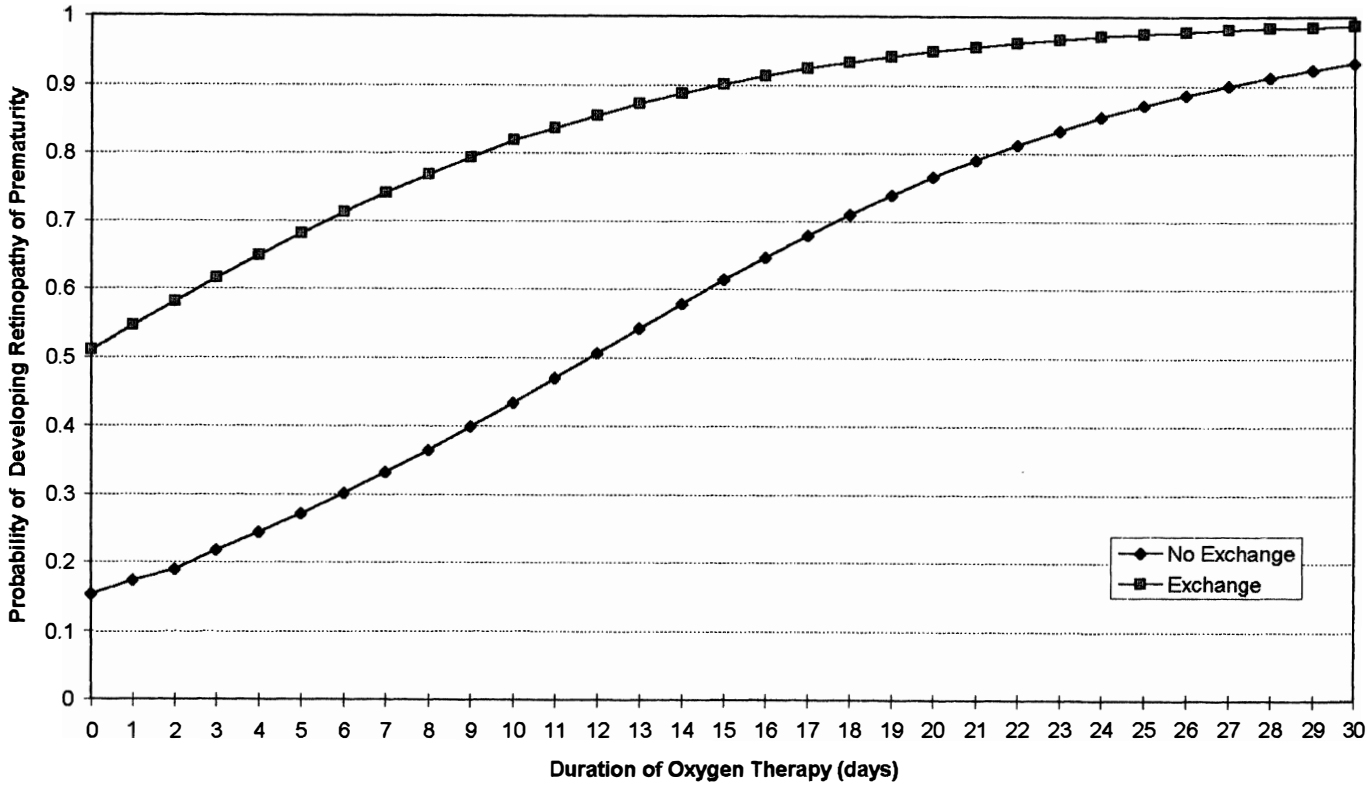

Fig. 1. *The probability of developing retinopathy of prematurity in relation to oxygen therapy and exchange transfusion.*

study it was difficult to enforce uniform timing of the eye examination due to various problems such as the clinical condition of the infants while in hospital and the follow-up of the infants after discharge. As the mortality rate in our patients before discharge was high, the actual incidence of ROP may be higher than 31.9%. This may be one of the reasons why the incidence of ROP in this study is lower than that of other studies.[21–23] Unlike studies reported elsewhere, lower birthweight, younger gestational age at birth and the highest documented mean PaO_2 were not significant risk factors associated with the development of ROP in our patients.[8,12,13,15,16] One possible explanation for this discrepancy could be the relatively small number of patients with ROP in our study.

The results of our study confirmed, however, that the duration of oxygen therapy is an important risk factor associated with the development of ROP.[7] Our findings suggest that there is a need for continuous monitoring of VLBW infants on oxygen therapy and that supplemental oxygen therapy should be terminated as soon as possible when there is no further indication for it. The use of the chart which we have constructed (Fig. 1) for the prediction of development of ROP in VLBW infants following exposure to various durations of oxygen therapy will help neonatologists in developing countries to identify the very high risk infants for screening by the limited number of ophthalmologists in their countries.

The association between ROP and blood transfusions has been reported previously.[5,6,10] Blood transfusions provide the infants with a greater proportion of adult haemoglobin which readily releases oxygen to the tissues including the retina. Fetal haemoglobin, on the other hand, with its higher affinity for oxygen, tends to protect the retina from hyperoxaemia as it requires a higher PaO_2 before it releases its oxygen content. During exchange transfusion, much larger volumes (about 8–9 times of the volume used for replacement transfusion) of adult blood and haemoglobin are transfused into the infants. Thus, it is not surprising to find that exchange transfusion is a significant risk factor associated with ROP in our patients.

Even in the most modern neonatal units with sophisticated equipment and technology, ROP remains a problem. The role of oxygen in its pathogenesis remains an enigma. The problem is to define in a quantitative way its relationship to ROP. Our study shows that it is not just a simple factor of oxygen therapy. The duration of exposure to oxygen and ease of release of oxygen at the retinal level are significant risk factors associated with the development of ROP. There is, therefore, a need for close ophthalmological surveillance in VLBW babies, especially those who are subjected to prolonged oxygen therapy and exchange transfusion. While the practices of providing oxygen and exchange transfusion are often life-saving, a more judicious approach to the use of such therapies may help to reduce the

problem of ROP. As suggested by the multi-centre study on cryotherapy,[27] cryotherapy is advocated for those with stage 3 threshold disease.

Key words: Exchange transfusion, Oxygen therapy, Retinopathy of prematurity, Very low birthweight infants.

REFERENCES

1. Flynn JT. Retrolental fibroplasia: an update. In: Caldwell DR, Baxter R, Carisa D, Wool B, editors. Paediatric ophthalmology and strabismus: transactions of the New Orleans Academy of Ophthalmology. New York: Raven Press, 1986:293–325.
2. Fielder AR, Levene MI. Screening for retinopathy of prematurity. Arch Dis Child 1992;67:860–7.
3. Ashton N, Ward B, Serpell G. Role of oxygen in the genesis of retrolental fibroplasia. Br J Ophthalmol 1953;37:513–20.
4. Gunn TR, Easdown J, Outerbridge EW, Aranda JV. Risk factors in retrolental fibroplasia. Paediatrics 1980;65:1096–100.
5. Yu VHY, Hookham DM, Nave JRM. Retrolental fibroplasia: controlled study of 4 years' experience in a neonatal intensive care unit. Arch Dis Child 1982; 57:247–52.
6. Clark C, Gibbs JAH, Maniello R, Outerbridge EW, Aranda JV. Blood transfusion: a possible risk factor in retrolental fibroplasia. Acta Paediatr Scand 1981; 70:535–9.
7. Gallo JE, Jacobson L, Broberger U. Perinatal factors associated with retinopathy of prematurity. Acta Paediatr 1993;82:829–34.
8. Prendiville A, Schulenburg WE. Clinical factors associated with retinopathy of prematurity. Arch Dis Child 1988;63:522–7.
9. Hammer ME, Mullen PW, Ferguson JG, Pai S, Cosby C, Jackson KL. Logistic analysis of risk factors in acute retinopathy of prematurity. Am J Ophthalmol 1986; 102:1–6.
10. Shohat M, Reisner SH, Krikler R, Nissenkorn I, Yassur Y, Ben-Sira I. Retinopathy of prematurity: incidence and risk factors. Paediatrics 1983;72:159-63.
11. Spires R. Retinopathy of prematurity. J Ophthalmic Nurs Technol 1991;10:166–70.
12. Yu VY, Lim CT, Downe LM. A 12-year experience of retinopathy of prematurity in infants less than or equal to 28 weeks gestation or less than or equal to 1000 grams birthweight. J Paediatr Child Health 1990; 26:205–8.
13. Charles JB, Ganthier R Jr, Appiah AP. Incidence and characteristics of retinopathy of prematurity in a low-income inner-city population. Ophthalmology 1991; 98:14–7.
14. Fielder AR, Robinson J, Shaw DE, Ng YK, Moseley MJ. Light and retinopathy of prematurity: does retinal location offer a clue? Paediatrics 1992;89:648–53.
15. Darlow BA, Horwood LJ, Clemett RS. Retinopathy of prematurity: risk factors in a prospective population-based study. Paediatr Perinat Epidemiol 1992;6:62–80.
16. Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, Tung B. Incidence and ealy course of retinopathy of prematurity: the cryotherapy for retinopathy of prematurity cooperative group. Ophthalmology 1991;98:1628–40.
17. Flynn JT, Bancalari E, Snyder ES, Goldberg RN, Feuer W, Cassady J, Schiffman J, Feldman HI, Bachyuski B, Buckley E, *et al.* A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med 1992;326:1050–4.
18. Glass P, Avery GB, Subramaniam KNS, Keys MP, Sostek AM, Friendly DS. Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. N Engl J Med 1985;313:401–4.
19. Ackerman B, Sherwonit E, Williams J. Reduced incidental light exposure: effect on the development of retinopathy of prematurity in low birthweight infants. Paediatrics 1989;83:958–62.
20. Flynn J. The premature retina: a model for the *in vivo* study of molecular genetics? Eye 1992;6:161–5.
21. Reisner SH, Amir J, Shohat M, Krikler R, Nissenkorn I, Ben-Sira I. Retinopathy of prematurity: incidence and treatment. Arch Dis Child 1985;60:698–701.
22. Schaffer DB, Johnson L, Quinn GE, Weston M, Bowen FW. Vitamin E and retinopathy of prematurity. Ophthalmology 1985;92:1005–11.
23. Ng YK, Fielder AR, Shaw DE, Levene MI. Epidemiology of retinopathy of prematurity. Lancet 1988; 4:1235–8.
24. Ballard JL, Novak KK, Denver M. A simplified score for assessment of fetal maturation in newborn infants. J Paediatr 1979;95:769–74.
25. Silverman WA, Anderson DA. A controlled clinical trial of effects of water mist on obstructive respiratory signs, death rates and necropsy findings among premature infants. Paediatrics 1956;17:1–10.
26. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984;102: 1130–4.
27. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol 1988;106:471–9.