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Risk Factors for Retinopathy of Prematurity

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Abstract: Objective Retinopathy of prematurity (ROP) is one of important causes of childhood visual impairment and blindness. Many research has shown that low birth weight (BW) and low gestational age (GA) are primary risk factors for ROP. This paper aims at studying the other high risk factors involved in the development of ROP. **Methods** Sixty-four preterm infants with and without ROP were divided into two groups: a ROP group and a control group without ROP (n = 32 for each). The clinical data of the two groups were studied by case-contrast study according to the paired design of GA and BW. Logistic regression analysis was done for 20 possible risk factors. **Results** The odds ratios of the duration of oxygen therapy (DOT), maximal PaO_2 ($MaxPaO_2$), pregnancy induced hypertension (PIH) and minimum pH value within the first 3 days of life (MinpH) were 2.764, 2.175, 1.935 and 2.417 respectively ($P < 0.01$). The logistic regression equation of the risk factors in preterm infants with ROP was Logit (P) = β_0 + 1.265 DOT + 1.034 Max PaO_2 + 0.936 PIH - 1.273 MinpH ($\chi^2 = 25.634$, $P < 0.01$). **Conclusions** The long time of oxygen exposure, hyperoxia, PIH and acidosis are high risk factors in the development of ROP.

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Key words: Retinopathy of prematurity; Risk factor; Preterm infant

早产儿视网膜病危险因素分析

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[**摘 要**] **目的** 早产儿视网膜病(ROP)是儿童视觉损害及致盲的重要原因之一。众多的研究表明低出生体重和低胎龄是 ROP 发病的主要危险因素。该文旨在探讨除出生体重和胎龄外,影响 ROP 发生的其他危险因素。**方法** 根据胎龄、出生体重进行配对,合并 ROP 的早产儿和未合并 ROP 的早产儿各 32 例进行对照研究,对 20 种可能的危险因素进行 Logistic 回归性分析。**结果** 氧疗时间(DOT)、最高动脉氧分压($MaxPaO_2$)、妊娠高血压(PIH)、生后 3 d 内最低 pH 值(MinpH)的比值比(OR)值分别为 2.764、2.175、1.935、2.417($P < 0.01$)。建立的早产儿 ROP 危险因素主效应模型是 Logit(P) = β_0 + 1.265 DOT + 1.034 $MaxPaO_2$ + 0.936 PIH - 1.273 MinpH ($\chi^2 = 25.634$, $P < 0.01$)。**结论** 氧疗时间长、高氧血症、妊娠高血压和酸中毒为 ROP 的高危因素。

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[**关 键 词**] 早产儿视网膜病;危险因素;早产儿

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Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the eye. ROP has been recognized as an important cause of childhood, visual impairment and blindness since the 1940s when improved facilities and treatment increased the survival rate of premature infants. Although its incidence and severity have been decreasing in developed countries over the past two decades, both are increasing in developing countries[1]. Many research has shown that low birth weight (BW) and low gestational age (GA) are primary risk factors for ROP. Severe ROP is usually found in babies with a GA of less than 26 weeks,

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and the incidence and severity are inversely proportional to GA. Besides BW and GA, many other risk factors associated with ROP have been proposed. This paper studies the other high risk factors involved in the development of ROP according to the paired design of BW and GA.

Materials and methods

Subjects

Sixty-four preterm infants (37 males and 27 females) admitted to Chonnam University Hospital in Korea between January, 1999 and January, 2001 were enrolled in this study. Of them, there were 32 preterm infants with ROP and with GA of (28 ±3.2) weeks and BW of (963 ±287) g (ROP group), and they were matched with the other 32 preterm infants without ROP (control group) who had the similar GA and BW as the ROP group [GA = (28 ±3.4) weeks; BW = (980 ±238) g]. There was no significant difference in either GA or BW between the two groups.

Diagnostic criteria

ROP was diagnosed when the morphologic changes of retinal vascular occurred along the junction of vascularization and unvascularization of peripheral retina, and classified in grades 1 to 5 according to the international classification[2].

Risk factors for ROP

The possible risk factors for ROP included 20 items: the duration of oxygen therapy (DOT), 1 minute Apgar scores (Apgar 1), 5 minutes Apgar scores (Apgar 5), the duration of mechanical ventilation (DMV), the minimum PaO_2 (MinPaO_2), the maximum PaO_2 (MaxPaO_2), the maximum $PaCO_2$ (Max$PaCO_2$), surfactant replacement therapy, pregnancy-induced hypertension (PIH), apnea, treatment with indomethacin, bradycardia, respiratory distress syndrome, intraventricular hemorrhage, anemia, hypothermia, exchange transfusion, hypotension, the minimum pH value within the first 3 days of life (MinpH) and the maximum inspiratory oxygen concentration.

Statistical analysis

The *t* test was used for quantitative variables and χ^2 test for qualitative variables. Logistic regression analysis was done for the variables with statistical significance and to establish regression model. All the data were analyzed by the SPSS 10.0 software.

Results

Single factor analysis between the ROP group and the control group

After the single factor analysis for the above 20 possible risk factors were done, it was found that 6 risk factors, including DOT, Apgar 1, DMV, MaxPaO_2, PIH and MinpH were significantly different between the two groups ($P < 0.05$ or 0.01) (Table 1).

Table 1 Comparison of risk factors between the ROP group and the control group (n = 32, $\bar{x} \pm s$)

Groups	DOT(d)	Apgar 1	DMV(d)	MaxPaO_2(mmHg)	PIH(%)	MinpH
ROP	29 ±3.5	3.6 ±1.2	18.7 ±5.4	108 ±15	38	6.983 ±0.231
Control	21 ±4.7	5.4 ±1.5	14.2 ±4.3	88 ±12	14	7.134 ±0.247
t	3.176	-3.468	2.178	3.765		-3.673
χ^2					4.358	
P	<0.01	<0.01	<0.05	<0.01	<0.01	<0.01

Logistic regression analysis of the risk factors for ROP

Of the 6 risk factors (variables), 4 variables, DOT, MaxPaO_2, PIH and MinpH were brought into the best regression equation by logistic stepwise regression analysis (Table 2). The equation of the risk factors for ROP in preterm infants was Logit (P) = β_0 + 1.265 DOT + 1.034 MaxPaO_2 + 0.936 PIH - 1.273 MinpH (χ^2 = 25.634, $P < 0.01$). It was found that there was statistical significance in this model.

Table 2 Main parameters of logistic regression model of risk factors for ROP

Variables	β	Odds ratio	95 % CI	*P*
DOT	1.265	2.764	1.873 - 3.298	< 0.01
MaxPaO_2	1.034	2.175	1.638 - 3.046	< 0.01
PIH	0.936	1.935	1.374 - 2.941	< 0.01
MinpH	- 1.273	2.417	1.742 - 3.190	< 0.01

Discussion

In many predisposing factors for ROP, low BW and low GA are proposed as primary ones, and the others may have effects on the development of ROP. The 20 possible risk factors in this study have been reported to be associated with ROP[3,4]. This study aims at exploring the high risk factors so that ROP can be prevented. The multiple logistic regression analysis in this research showed that DOT, Max-PaO_2, PIH and MinpH were the other high risk factors besides GA and BW.

ROP in relation to supplemental oxygen has been established. The controversy issue is what effects the amount and timing of oxygen therapy will have on the incidence and severity of this disorder. The wide fluctuations of oxygen saturation levels may have effects on the development and progression of ROP. Under hyperoxic conditions, excess oxygen moves from the choroidal to the retinal circulation, bathing the retina and constricting the retinal vessels[5]. In the rat model both hypoxia and unstable oxygen levels are important causes of ischemic retinopathy[6]. Chronic intrauterine ischemic-hypoxia has been associated with ROP[7]. PIH as the high risk factor in this study suggests that PIH may lead to intrauterine ischemic-hypoxia and induce retina vasoproliferation.

Chen[8] reported periods of systemic acidosis as brief as 24 hours were associated with preretinal neovascularization in the newborn rat model of ROP. This study demonstrated that the MinpH was the high risk factor, suggesting systemic acidosis may damage the development of retinal vasculature and induce neovascularization.

The WHO's Vision 2020 programme targets ROP as an "avoidable disease" and requires early detection and treatment for this disorder to prevent blindness[9]. Current treatment options for ROP are expensive and may have potentially serious complications, thus prevention is still the best strategy available at present. Therefore, attention must be directed towards (1) carefully monitoring levels of supplemental oxygen when necessary, and maintaining PaO_2 of 6.7 - 9.3 kPa; (2) decreasing incidence of hypoxia, hyperoxia and acidosis and (3) prevention and treatment pregnancy-induced hypertension syndrome.

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