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The Most Important Factors for Retinopathy of Prematurity in Preterm Infants

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Purpose : There are many known risk factors for a retinopathy of prematurity (ROP). We analyzed the most important risk factors and predictors of ROP among them.

Methods : We retrospectively reviewed the medical records of all premature infants admitted to the neonatal intensive care unit (NICU), between January 2010 and December 2012 at Gangnam CHA Medical Center, Seoul. . All infants (n=185) were hospitalized for more than 28 days, received eye examination for ROP and showed one of the following criteria: birth weight (BW) below 1,500 g, gestational age (GA) below 32 weeks, or oxygen treatment (≥40% oxygen for more than 3 days). We divided the infants into the Non-ROP group (n=162) and the ROP group (n=23, more than stage 1) and analyzed group comparisons, risk factors and the importance of each factor of ROP by SPSS 13.0.

Results : Risk factors were duration of oxygen uses [Odds ratio (OR): 1.064, 95% confidence interval (CI): 1.007-1.125, *P*=0.028] and intravenous (IV) steroid (OR: 1.234, 95% CI: 1.000-1.523, *P*=0.049) by multi-factor adjustment. The most important factor was oxygenation duration. The following factors were time to full enteral feedings, and IV steroid duration.

Conclusion : The incidence of ROP will be decreased if we can reduce the length of oxygen uses, IV steroid use and advance the full feeding achievement.

Key Words : Retinopathy of prematurity, Risk factor, Oxygen, Enteral feeding, Steroid

Retinopathy of prematurity (ROP) is the leading cause of blindness in children with a birth history of low birth weight and preterm.[1] Unlike in almost all term infants whose retina and retinal vasculature are fully developed and ROP cannot occur. In preterm infants, the development of the retina, which proceeds from the optic nerve head anteriorly during the course of gestation, is incomplete, with the extent of immaturity of the retina mainly depending on the degree of prematurity at birth. The incidence of ROP has risen with the increasing rate of survival of infants with very low birth weight (VLBW) or low gestational age.

In general, multiple systemic risk factors of ROP are known and include low gestational age, low birth weight and oxygen treatment as the major risk factors.[2-4] Recently, many studies worldwide focused that an early diagnosis could improve the success rate of treatment and reduce complications of ROP. Also, most clinical physicians try to reduce the risk factors of ROP. We thought if there were many risk factors, there would be important factors which strongly influence ROP. It may be helpful for the prevention of ROP in preterm infants if we know the important factors. So, we analyzed the risk factors and the

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important factors of ROP in preterm infants.

Materials and Methods

We retrospectively reviewed the medical records of all premature infants who were admitted to the neonatal intensive care unit (NICU) at Gangnam CHA Medical Center of Seoul between January 2010 and December 2012. All infants with birth weight (BW) below 1,500 g or gestational age (GA) below 32 weeks or oxygen treatment (≥40% oxygen for more than 3 days), who were hospitalized for more than 28 days and received eye examinations for ROP were enrolled in our study (n=185). Infants with cardiac, respiratory, neurological or ocular anomalies (except ROP) or genetic diseases and infants who died before eye examination were excluded.

The first eye examination was performed by a well-trained ophthalmologist at a postmenstrual age (PMA) of 31 to 36 weeks by indirect ophthalmoscopy, following the guideline of the American Academy of Pediatrics (AAP).[5] The repeated examinations and reports were performed by decision of the ophthalmologist, depending on the severity of the disease. ROP was classified according to the International Classification of Retinopathy of Prematurity (ICROP).[6]

We divided the infants into a non-ROP group and a ROP group (more than stage 1). Data derived from the medical files included gestational age, birth weight, gender, type of pregnancy (singleton/multiple), Apgar scores (APGA) at 1 minute and 5 minutes, blood platelet count at birth day, proven sepsis confirmed by positive blood cultures,[7] respiratory distress syndrome (RDS), respiratory data including duration of oxygen and intubation treatment, postnatal intravenous (IV) steroid duration, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC, ≥ stage II by modified Bell' s stage),[8] intraventricular hemorrhage (IVH, ≥ grade II by Papile staging),[9] bronchopulmonary dysplasia (BPD, by NIH workshop grading),[10] red cell blood (RBC) transfusion times, duration of total parenteral nutrition (TPN), and time of achievement of full enteral feeding (enteric feeding ≥100 cc/kg/day). The documented perinatal variables included the presence of clinical chorioamnionitis, prolonged rupture of membrane (PROM), preeclampsia, multiple births, in vitro fertilization (IVF), and prenatal betamethasone usage. Clinical chorioamnionitis was defined according to the criteria proposed by Gibbs et al,[11] which include an elevation of body temperature >37.8℃ and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leukocytosis (>15,000/mm^3), maternal tachycardia (>100 beats/min), and fetal tachycardia (>160 beats/min).

Data were analyzed by the Statistical Package for the Social Sciences (SPSS for windows, version 13.0). Group comparisons were done by *t*-tests between 2 groups, logistic regression model was used to determine the contributing factors of ROP and the importance of each factor was estimated using SPSS Tree program.

Results

There were 23 of 185 infants in the ROP group (12.4%); 15 infants (8.1%) developed a mild ROP (stage 1 and 2) and 8 infants (4.3%) were diagnosed with severe ROP (≥stage 3). The birth weight varied between 750 and 2,900 g. The range of gestational age was between 26 and 36 weeks.

There was a significant difference in the mean birth weight and the mean gestational age in preterm infants with and without ROP (Table 1). The ROP

Table 1. Clinical characteristics of VLBW infants

	Non-ROP (n=162)	ROP (n=23)	*P*-value
GA (weeks)	31.4±2.2	28.8±2.0	0.000
BW (g)	1,648.1±411.7	1,232.2±346.4	0.000
Male (n)	96 (59%)	12 (52%)	NS
APGA at 1-minute	4.8±1.7	3.8±2.0	0.033
APGA at 5-minute	6.6±1.4	5.7±1.7	0.018
Platelet count (10^3/μL)	223.1±60.2	215.7±58.7	NS
Proven sepsis (n) *	4 (3%)	3 (13%)	NS
RDS (n)	115 (71.0)	22 (95.7)	0.000
PDA (n)	39 (24%)	8 (35%)	NS
NEC (n)	12 (7%)	5 (22%)	NS
IVH (n)	71 (44%)	9 (39%)	NS
BPD (n)	10 (6%)	4 (18%)	NS
RBC transfusion (n)	1.4 (1.8%)	3.4 (2.2%)	0.000
IV steroid (d)	0.9±2.0	3.0±4.2	0.028
Ventilator treatment (d)	4.8±7.7	11.7±11.6	0.011
Oxygen uses (d)	15.9±14.0	41.1±22.6	0.000
TPN (d)	22.0±13.4	32.2±14.1	0.003
Day of full feeding (d)	26.3±13.4	33.9±14.4	0.025
Hospital day (d)	41.2±16.8	51.4±19.4	0.008

* Including blood culture positive
Abbreviations: VLBW, very low birth weight; ROP, retinopathy of prematurity; GA, Gestational age; BW, Birth weight; APGA, apgar score; RDS, Respiratory distress syndrome; PDA, Patent ductus arteriosus; NEC, Necrotizing enterocolitis; IVH, Intraventricular haemorrhage; BPD, Bronchopulmonary dysplasia; RBC, Red blood cell; IV, Intravenous; TPN, Total parenteral nutrition, NS, non-significant
Values are expressed as number (percent) or mean±standard deviation

group showed significantly lower Apgar scores at 1 minute and 5 minutes than the Non–ROP group. RDS, RBC transfusion and TPN duration were significantly higher in the ROP group than in the Non–ROP group. Infants of the ROP group showed significantly more days of intubation and oxygen treatment, and postnatal IV steroid duration than the Non–ROP group. Also, the ROP group had a significantly longer time until achievement of full feeding and prolonged hospital days than the Non–ROP group. However, gender, platelet count, proven sepsis, PDA, NEC, IVH, and BPD were not different between both groups.

Table 2 shows maternal and obstetric factors in relation to the occurrence and progression of ROP. There was no significant association with the occurrence of ROP in the variables clinical chorioamnionitis, PROM, preeclampsia, multiple births and antenatal betamethasone usage.

Table 2. Maternal and obstetric factors and comparison of variables

	Non-ROP (n = 162)	ROP (n = 23)	*P*-value
Clinical chorioamnionitis	69 (43%)	11 (42%)	NS
PROM	53 (33%)	12 (52%)	0.067
Preeclampsia	35 (22%)	3 (13%)	NS
Multiple births	72 (44%)	14 (61%)	NS
IVF	59 (36%)	7 (30%)	NS
Antenatal betamethasone	109 (68%)	14 (61%)	NS

Abbreviations: ROP, retinopathy of prematurity; PROM, Premature rupture of membranes; IVF, In vitro fertilization; NS, nonspecific
Values are expressed as number (percent)

A multiple regression analysis was performed with the statistically significant risk factors in which an association with ROP occurrence was identified after

controlling for potential risk factors (Table 3). Oxygen duration in hospital days [odds ratio (OR) =1.064; 95% confidence interval (CI), 1.007–1.125; P=0.028] was independently associated with ROP occurrence. The or of IV steroid use duration was 1.234 (95% CI, 1.000–1.523; P=0.049), but gestational age and birth weight were not independently associated with ROP occurrence.

Table 4 shows the importance of independent variable of the significant risk factors. Duration of oxygen uses was the risk factor with the highest importance, followed by time of achievement of full feeding and IV steroid duration.

Table 3. The odds ratio of retinopathy of prematurity by logistic regression

Variable	Odds ratio	95% CI	*P*-value
GA	0.742	0.443–1.242	0.257
BW	0.999	0.996–1.002	0.390
RBC transfusion	0.377	0.051–2.816	0.342
IV steroid	1.234	1.000–1.523	0.049
Duration of oxygen uses	1.064	1.007–1.125	0.028
Full feeding day	1.043	0.958–1.137	0.333

Adjustment factors: APGA at 1 min and 5 min, RDS, TPN
Abbreviations: CI, confidence interval; GA, gestational age; BW, Birth weight; RBC, red blood cell; IV, intravenous; APGA, apgar score; RDS, respiratory distress syndrome; TPN, Total parenteral nutrition

Table 4. The importance of risk factors of retinopathy of prematurity

Independent variable	Importance	Normalized importance
Oxygen Duration	.072	100.0%
Full Feeding	.063	88.2%
IV Steroid	.042	59.4%
GA	.025	34.3%
RBC transfusion	.017	23.2%
APGA at 5 min	.003	4.6%
APGA at 1 min	.002	2.3%

Growing Method: CRT
Dependent Variable: Presence or absence of ROP
Abbreviations: IV, intravenous; GA, gestational age; RBC, red blood cell; APGA, apgar score

Discussion

ROP is a disorder of retinal vascular development in preterm infants. It continues to be a significant complication in preterm neonates and remains a major cause of childhood blindness worldwide despite of advances in neonatal care.[12]

ROP is known as a multifactorial disease generally involving many factors. Its major known risk factors are low gestational age, low birth weight and oxygen treatment.[2–4] Additionally, there are many risk factors such as sepsis, respiratory diseases, surfactant usage, hypotension, PDA, NEC, fetal hemorrhage, IVH, red cell blood transfusion times, postnatal steroid usage, duration of TPN, less breast feeding, poor weight gain, preeclampsia, prolonged rupture of membrane (PROM), maternal pyrexia and maternal betamethasone usage.[2, 7, 8, 13–18] The data of our study showed that the ROP group had statistically significant lower BW, GA and APGA than the Non-ROP group. And they showed a higher incidence of RDS, longer durations of oxygen, intubation and mechanical ventilation, postnatal IV steroid duration, TPN, and hospital day than the Non-ROP group. In our study, postnatal IV steroid duration and oxygen treatment duration including mechanical ventilation were the risk factors of ROP after adjusting for multifactor. These two factors might be regarded as indicators of respiratory diseases needing treatment.[19] The occurrence of respiratory diseases such as RDS and BPD, which require ventilation care or supplemental oxygen support, or IV steroid duration, was also significantly higher in those who developed ROP. Since the incidence of ROP rose with the increasing duration of low-dose oxygen therapy as well as high-dose oxygen therapy, the period of low-dose

oxygen therapy needs to be shortened to prevent an occurrence of severe ROP and its rapid progression.[13] A few previous studies have shown an independent association of ROP with the prolonged use of postnatal steroids[20] as well as with prolonged ventilation or oxygen treatment, conditions that may be closely related to the development of chronic lung disease.[19] Based on these data, we suggest that oxygen and postnatal steroid usage control may be one of the important preventative strategies for an avoidance of ROP incidence.

Our study confirmed the risk factors of ROP known from previous studies and identified the important factors among the risk factors of ROP. Duration of oxygen uses was the most important factor and time of achievement of full feeding and duration of postnatal IV steroid usage were the 2nd and the 3rd important factor that could be identified as significant factors by the statistically alternative statistical model, although time of achievement of full feeding was not a significant risk factor in the logistic regression. The number of days on parenteral nutrition maintained until achievement of the full feeding is an indicator of feeding difficulties. Therefore, the improvement of enteral feeding is likely to be eventually preparative strategies for an avoidance of ROP incidence.

Most clinicians have tried to reduce the incidence of ROP due to analysis of risk factors. In this present study, we suggest the important factors of ROP development. The incidence of ROP will be decreased if we can reduce the length of oxygen treatment, IV steroid use, and advance the full feeding achievement.

Conflict of interest

No potential conflict of interest was reported relevant to this article.

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미숙아 망막병증의 중요 위험인자

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목적 : 본 연구에서는 32주 미만의 극소 저체중 출생아에서 미숙아 망막병증의 위험요인 가운데 중요한 예측 인자를 분석하고자 하였다.
방법 : 2010년부터 2012년까지 강남차병원 신생아 중환자실에 28일 이상 입원하고, 출생 체중 1,500 g 미만이거나 재태주령 32주 미만, 혹은 3일 이상 40% 이상의 산소농도로 치료 받은 기왕력이 있는 미숙아 185명을 미숙아 망막증 진단 받은 군(23명, stage 1 이상)과 받지 않은 군(162명)으로 나누고 의무기록을 이용해 후향적으로 비교하고 분석하였다.
결과 : 산소치료 기간 [Odds ratio (OR)=1.064; 95% confidence interval (CI) 1.007-1.125; *P*=0.028]과 출생 후 정맥 스테로이드 사용 기간 (OR: 1.234, 95% CI: 1.000-1.523, *P*=0.049)이 다변량 분석을 사용했을 때 유의한 위험요인이었다. 가장 중요한 위험요인은 산소치료 기간이었으며, 그 밖에 장관 영양이 완료된 시점과 정맥 스테로이드 사용 기간이 있었다.
결론 : 산소치료 기간과 정맥 스테로이드 사용 기간을 줄이고, 장관 영양을 도모함으로써 미숙아 망막증의 발생률을 낮출 수 있을 것으로 사료된다.

중심 단어 : 미숙아 망막증, 위험요인, 산소, 장관 영양, 스테로이드