A Retrospective Analysis of Retinopathy of Prematurity (ROP) in a Tertiary Newborn Intensive Care Unit: Incidence and Risk Factors of ROP

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Abstract

Background Retinopathy of prematurity (ROP) is the most frequent problem which causes blindness in preterm babies. In our study we evaluate the frequency of retinopathy, the risk factors, and their effects on disease development in premature newborns admitted to our neonatal intensive care unit (NICU).

Methods A total of 139 premature infants with gestational ages less than 34 weeks followed in our NICU between January 1, 2008 and January 1, 2011. The infants were divided into two groups as group 1 (no ROP/mild ROP) and as group 2 (severe ROP).

Results The demographics of 139 patients were as follows: 79 (56.83%) were female and 60 (43.17%) were male. Overall, 104 (74.8%) patients were found to have no or mild ROP and 35 (25.2%) had severe ROP. Among the patients in the severe ROP group, 25 of them had plus disease. With logistic regression analysis, lower gestational age (odds ratio [OR]: 4.1, confidence interval [CI]: 1.9–9.2), the central catheter usage (OR: 13.4, CI: 1.2–146.6), hypotension (OR: 7.5, CI: 1.1–49.6), perinatal asphyxia (OR: 261.3, CI: 8.8–7725.4), apnea (OR: 18.1, CI: 1.6–202.6), and high FiO_2 (OR: 1.2 CI: 1.0–1.5) were found to be related to severe ROP.

Conclusion Among the preterms with very low body weight included in our study, we found that the frequency of severe ROP requiring treatment was low. The most important factors related to severe ROP were found to be low gestational age and birth weight. Being aware of the risk factors related to severe ROP in addition to screening every preterm infant carrying these risk factors is extremely important for the early diagnosis and treatment to prevent blindness due to severe retinopathy.

Keywords
- NICU
- ROP
- prematurity

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Introduction

Retinopathy of prematurity (ROP) is a disease characterized by abnormal proliferation of retinal vessels in preterm babies and those with low birth weight (BW).[1] Today, it is one of the most dramatic problems of neonatology and the most frequent cause of blindness in children.[2] Frequency of ROP is also affected by the development level of communities and quality of newborn care. In developing and underdeveloped countries, it is reported that the incidence of the disease is increasing and severe retinopathy is seen in more mature preterms as a result of failure in diagnosis and management of ROP due to shortages of both medical experts and essential equipment in neonatal intensive care units (NICUs).[3] Major risk factors associated with the occurrence of premature retinopathy are gestational age (GA) and BW. Other known factors include hypoxia, oxygen therapy, maternal preeclampsia, pulmonary hemorrhage, ventilation time and continuous positive pressure ventilation, intraventricular bleeding, apnea, sepsis, hypercarbia, acidosis, bronchopulmonary dysplasia (BPD), and blood transfusion.[4,5] Therefore, it is important to recognize the risk factors and apply screening and treatment programs to prevent permanent visual damage.

In our study, we aimed to evaluate the frequency of retinopathy in premature newborns observed in our level III NICU, along with the risk factors and their effects on disease development.

Methods

Our study had 139 premature babies treated in an obstetrics and gynecology training and research hospital NICU between January 1, 2008 and January 1, 2011. It was approved by the ethics committee. Ethics committee approval was received from local ethics committee.

Study Population

The medical records of newborns were analyzed retrospectively and documented in a form including maternal and neonatal clinical features. Patients were divided into two groups as mild ROP/non-ROP (group 1) and severe ROP (group 2). To evaluate the frequency of ROP patients were divided into three groups according to their BW as $<1{,}000$, 1,000 to 1,500, and $>1{,}500$ g, respectively. Likewise, cases were classified in three groups according to the GA as <28, between 28 and 32, and between 32 and 34 weeks. Newborns with congenital anomalies, chromosomal abnormalities, and those who died before the first ophthalmic examination were excluded from the study.

Clinical Characteristics

The GA was based on the mother's last menstrual date, ultrasound measurements, and the modified Ballard scoring performed within the first 24 hours.[6] Newborns were assessed according to the BW by using the Fenton intrauterine growth curves.[7] Antenatal and natal risk factors including maternal age, usage of antenatal corticosteroids, preeclampsia/eclampsia, infants of diabetic mothers, chorioamnionitis (clinical or histopathological), in vitro fertilization, multiple births, and mode of delivery were recorded from the mothers' files. Postnatal risk factors for the development of ROP such as intracranial hemorrhage (according to the classification of Papile et al[8]) resuscitation in the delivery room, respiratory distress syndrome (RDS), surfactant treatment, duration of invasive/noninvasive mechanical ventilation and oxygen therapy, patent ductus arteriosus (PDA), neonatal sepsis (clinically proven or culture positive), necrotizing enterocolitis (NEC) (in accordance with the Bell criteria[9]), and BPD (according to the oxygen requirement at 36 weeks postmenstrual age or 28 days after birth[10]), were recorded for each patient. From the records of these infants, the growth data and the medical history (both at birth and at each follow-up examinations in early life) were analyzed by computer and the day patients regain their BW after birth is described as catch-up BW time.

Ophthalmic Examinations

The International Classification of ROP was used to evaluate the stage of retinopathy.[11] The first ophthalmological examinations of the patients were performed between the fourth and sixth weeks after birth. Patients who did not have ROP during the first examination, along with whose retinal vascularization was not completed, were followed up with an interval of 2 to 4 weeks, and the patients who had stage 1 or stage 2 ROP were followed up with an interval of 1 to 2 weeks until vascularization was completed. Patients developing retinopathy were divided into two groups as mild ROP/non-ROP and severe ROP. Severe ROP was defined as advanced stage ROP requiring laser therapy, any stage in zone I with plus disease, zone I stage 3 without plus disease, and zone II stage 2 or 3 with plus disease, respectively.

Criteria for treatment of ROP were based on the Early Treatment for Retinopathy of Prematurity study,[12] treatment options were laser photocoagulation, intravitreal bevacizumab, and vitreoretinal surgery. Because our hospital only had one ROP diagnosis facility at that time, we referred those patients who required treatment to another medical faculty hospital, and we followed those patients after their treatment together with ophthalmologists of the university hospital.

Statistical Analyses

Statistical analyses were done by using SPSS statistical software for Windows, 20.0. Numbers, frequencies (%), ratio, medians, and standard deviation values were used in the descriptive statistics of the data. The distribution of variables was checked with the Kolmogorov–Smirnov test. During the analysis of quantitative data, *t*-tests and Mann–Whitney *U* tests were used. The chi-square test was used to compare categorical variables, and the Fischer's test was used when chi-square conditions could not be met. Statistically significant risk factors in univariate analyses were evaluated and

the effect levels were investigated using a multivariate logistic regression model. Using logistic regression analyses variables with a $p \leq 0.05$ were accepted as independent risk factors. The odds ratio (OR) and 95% confidence interval (CI) for each risk factor were determined. Results were evaluated with 95% CI and at $p < 0.05$ significance level.

Results

The data of 139 preterm infants with a GA $\leq$ 34 weeks, who met the criteria of this study, and were hospitalized at the maternity and gynecology training and research hospital NICU were recorded. In our study, 79 (56.83%) of our patients were female and 60 (43.17%) were male. Patients developing retinopathy were divided into two groups as mild ROP/non-ROP (group 1) and severe ROP (group 2). Overall, 104 (74.8%) patients were found to have no or mild ROP and 35 (25.2%) had severe ROP. There were 25 patients with plus disease in group 2 (►**Table 1**).

According to the GA, 39 (28%) patients were $\leq$28 weeks, 78 (56.2%) were between 29 and 32 weeks, and 22 (15.8%) were between 32 and 34 weeks. According to BWs, 27 (26.6%) patients were $\leq$1,000 g, 61 (43.88%) between 1,000 and 1,500 g, and 22 (29.5%) $\geq$ 1,500 g. Gender distributions of the patients between group 1 and group 2 was not statistically significant ($p = 0.455$). In group 2, the GAs of the patients were significantly lower ($p < 0.001$) than in group 1. Similarly, the gestational weights of the patients in group 2 were significantly lower ($p < 0.001$) than those in group 1 (►**Table 2**). The duration of hospitalization in group 2 (57.63 ± 23.51) was significantly higher than in group 1 (30.81 ± 19.71) ($p = 0.03$). We determined several risk factors such as catheter usage, blood transfusion, phototherapy, duration of mechanical ventilation, duration of oxygen therapy, high FiO_2 demand, apnea, hypotension, NEC, PDA, pulmonary bleeding, sepsis, RDS, perinatal asphyxia, BPD, postnatal steroid usage, and surfactant usage by using univariate analyses (►**Table 3**).

Table 1 Distribution and ratios for ROP in all patients

		n	%
ROP	No ROP/mild ROP	104	74.8
	Severe ROP	35	25.2
Mature		70	50.4
ROP zone	Zone 1	11	7.9
	Zone 2	27	19.4
	Zone 3	31	22.3
Stage	None	19	13.7
	Stage 1	25	18.0
	Stage 2	19	13.7
	Stage 3	6	4.3
Plus disease		23	16.5
Laser therapy		30	21.6
Cryotherapy		8	5.8
Medical treatment		9	6.5

Abbreviation: ROP, retinopathy of prematurity.
Note: Medical treatment: vascular endothelial growth factor.

In the reduced model, decline in GA (OR: 4.1, CI: 1.9–9.2), increase in catheter usage (OR: 13.4, CI: 1.2–146.6), hypotension (OR: 7.5, CI: 1.1–49.6), perinatal asphyxia (OR: 261.3, CI: 8.8–7725.4), high FiO_2 (OR: 1.2, CI: 1.0–1.5), and apnea (OR: 18.1, CI: 1.6–202.6) had a significant effect on the development of severe ROP (►**Table 4**).

In our study, 30 (21.6%) patients had laser therapy, 8 (5.8%) had cryotherapy, and 9 (6.5%) had medical therapy (►**Fig. 1**).

Discussion

Today, premature babies with extremely low BW at the boundary of immaturity have become viable with the developing science of neonatology and current approaches. Even

Table 2 Demographic characteristics for no ROP/mild ROP and severe ROP groups

		No ROP/Mild ROP		Severe ROP		
			n (%)		*n* (%)	*p*
Gender	Female		61 (58.7)		18 (51.4)	0.455
	Male		43 (41.3)		17 (48.6)	
Gestational age (wk)[a]	Mean $\pm$ SD	30.73 ± 2.12		27.51 ± 1.94		< 0.001
Gestational age groups[a]	$\leq$ 28 wk		15 (14.4)		24 (68.6)	< 0.001
	29–32 wk		67 (64.4)		11 (31.4)	
	33 $\geq$ wk		22 (21.2)		0 (0.0)	
Weight (g)[a]	Mean $\pm$ SD	1386.0 ± 340.00		961.4 ± 328.8		< 0.001
Weight groups[a]	1,000 g		15 (14.4)		22 (62.9)	< 0.001
	1,000–1,500 g		51 (49.0)		10 (28.6)	
	1,500 g		38 (36.5)		3 (8.6)	

Abbreviations: ROP, retinopathy of prematurity; SD, standard deviation.
[a]$p \leq 0.05$ level is statistically significant for no ROP/mild ROP and severe ROP.

Table 3 Postnatal risk factors for ROP

		Group 1	Group 2	*p*
Catheter, *n* (%)[a]		48 (46.2%)	29 (82.9%)	< 0.001
Blood transfusion, *n* (%)[a]		54 (51.9%)	31 (88.9%)	< 0.001
Phototherapy, *n* (%)[a]		82 (78.8%)	35 (100%)	0.003
Duration of MV (mean ± SD)[a]		5.81 ± 8.81	16.91 ± 13.55	< 0.001
Duration of O_2 therapy (mean ± SD)[a]		18.12 ± 18.06	42.91 ± 25.74	< 0.001
FiO_2 (mean ± SD)[a]		25.44 ± 4.42	34.28 ± 7.52	< 0.001
Apnea[a]		12 (11.5%)	24 (68.6%)	< 0.001
Hypotension[a]		33 (31.7)	25 (71.4%)	< 0.001
NEC[a]		8 (7.7%)	11 (31.4%)	< 0.001
PDA[a]		11 (10.6%)	11 (31.4%)	0.03
Pulmonary bleeding[a]		6 (5.8%)	11 (31.4%)	< 0.001
Sepsis[a]	None	63 (60.6%)	< 0.001	0.003
	Culture positive	24 (23.1%)	17 (48.6%)	
	Culture negative	17 (16.3%)	8 (22.9%)	
Perinatal asphyxia[a]		38 (36.5%)	23 (65.7%)	0.003
BPD[a]		10 (9.7%)	15 (42.9%)	< 0.001
Postnatal steroid[a]		10 (9.6%)	15 (42.9%)	< 0.001
Surfactant[a]		50 (48.1%)	33 (94.3%)	< 0.001
RDS[a]		52 (50.0%)	33 (94.3%)	< 0.001

Abbreviations: BPD, bronchopulmonary dysplasia; MV, mechanical ventilation; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SD, standard deviation.
[a]$p \leq 0.05$ level is statistically significant for no ROP/mild ROP and severe ROP.

Table 4 Reduced multivariate logistic regression

			95% confidence interval		
	β	OR	Lowest	Highest	*p*
Gestational age[a]	–1.422	4.1	1.9	9.2	S
Catheter[a]	2.2597	13.4	1.2	146.6	S
Duration of O_2 therapy[a]	0.051	1.1	1.0	1.1	S
Hypotension[a]	2.012	7.5	1.1	49.6	S
Perinatal asphyxia[a]	5.566	261.3	8.8	7725.4	S
FiO_2 mean[a]	0.214	1.2	1.0	1.5	S
Apnea[a]	2.896	18.1	1.6	202.6	S

Abbreviations: OR, odds ratio; ROP, retinopathy of prematurity; S, significant.
[a]$p \leq 0.05$ level is statistically significant for no ROP/mild ROP and severe ROP.

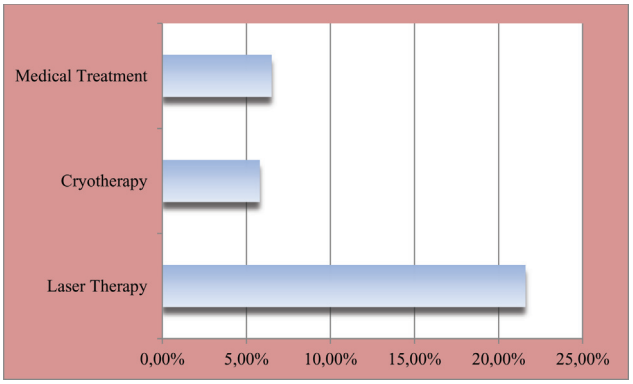

Fig. 1 Treatment modalities for retinopathy of prematurity (ROP).

though this situation increases the survival rates of preterm infants, it has also increased the long-term morbidities such as ROP. In many previous studies, numerous factors related to the development of ROP have been examined. The most important risk factors among these factors have been found to be low GA and BW.[13,14] In our study, we also found that the GA and BW of patients with severe ROP were statistically significantly lower ($p < 0.001$) in accordance with the previous studies. In the severe ROP group, 68.6% of the patients were < 28 weeks and 31.4% were between 29 and 32 weeks. No cases with severe ROP were found among preterm infants > 32 gestational weeks. Upon the evaluation of the cases according to BW, the incidence of severe ROP was found in 59.46% of infants born < 1,000 g, whereas 40.54% of these patients were found to have no ROP or mild ROP. Among our patients with a BW of > 1,500 g, 8.6% had severe ROP while 92.68% of these patients had no ROP or mild ROP. Many studies reported the incidence of ROP ranging from 50 to 82.2% in infants born < 1,000 g.[15,16] Compared with other studies' results, the number of patients with severe ROP, which may require laser and surgical treatment, is significantly lower in our study. We attribute this result to the less invasive interventions in our unit and the close follow-up of babies in terms of ROP development.

Current studies report different results about the distribution of patients with ROP according to the retinopathy stage. Palmer et al reported in their study that 25.2% of the patients had stage 1, 21.1% had stage 2, and 18.3% had stage 3 diseases in a large-scale study of 2,699 premature babies.[15] Furthermore, Fielder and Posner reported these rates in their study as 29.9, 16.3, and 6.4%, respectively.[17] In our study, 18% of our cases had stage 1, 13.7% had stage 2, and 4.3% had stage 3 diseases.

Many studies revealed that poor postnatal weight gain increases the risk and severity of ROP development. In a study from Sweden, the risk of serious ROP development was observed by monitoring the decrease in insulin-like growth

factor-1 serum levels in premature babies with the poor postnatal weight gain according to the WINROP algorithm.[18]

Similar to the common findings in the literature, we found that the duration of oxygen therapy in our patients with severe ROP was significantly longer than the other group. Furthermore, asphyxia, which is an important cause of hypoxia, was also evaluated as an independent risk factor for ROP development in our study. Many studies about ROP pathogenesis demonstrate the proven risks of oxygen administration and hyperoxia in early neonatal life. It is known that various free oxygen radicals are formed as a result of high oxygen levels, and these radicals disrupt the development of migrating spindle cells to form retinal vascularization.[19] Although oxygen supplementation is among the proven risk factors of ROP today, there is no definitive data on which treatment and concentration of oxygen will be effective on ROP. Also, oxygen supplementation is not a must for ROP development. Lucey and Dangman reported 95 babies who have never received oxygen therapy but developed ROP.[20] Today, the new approach is to implement different prevention strategies by considering different effects of oxygen in phase I (hyperoxic phase) and phase II (hypoxic phase) of ROP.

In our study, another risk factor for ROP development was blood transfusion. Infants requiring transfusions are also sicker and as a result of the blood transfusions (involving adult hemoglobin) to premature babies, oxygen that is already loosely attached to adult hemoglobin will be easily released and further damage the capillaries and disrupt their development.[21,22] Additionally, repeated transfusions may also cause free iron accumulation, which may result in increased production of free hydroxyl radicals as assessed by the Fenton reaction, resulting in damage to the retina.[23] Blood transfusion is accepted as a risk factor for ROP development in many studies while several studies have reported that a transfusion limitation could not reduce the prevalence of ROP.[24–26] Blood transfusion was found to be statistically significantly higher in patients with severe ROP than those in the other group in our study.

Sepsis is a multisystem disease caused by many risk factors such as hypotension which affects the frequency of ROP development in premature newborns.[27,28] Our study suggested that among the patients with severe ROP, clinical sepsis and culture-proven sepsis were found to be more frequently encountered compared with those in group 1. In addition, hypotension was found as an independent risk factor for severe ROP development by using multivariate logistic regression analyses.

Apnea attacks can lead to hypoxia, which may result in ROP development. There are studies in the literature defending that apnea attacks increase the risk of ROP development.[29,30] In our study, apnea episodes were also found to be a risk factor for ROP development both in the independent test and logistic regression analysis.

Previous studies suggested that ROP development rates are higher in infants who develop intraventricular hemorrhage (IVH), because of the hypoxic environment in peripheral retina.[31–33] We found no significant difference in the frequency of IVH among our patients between the two groups.

Treatment was performed in a total of 30 (21.6%) patients screened for ROP. A nationwide population-based study from the U.K. reported that diode laser photocoagulation was performed in 90.5% of infants requiring treatment.[34] In accordance with the previous studies, the main treatment modality in our patients with severe ROP was laser photocoagulation.

Limitation

Since it is a retrospective and single-centered study, our data are limited.

Conflict of Interest
None declared.

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