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Retinopathy of prematurity: incidence, risk factors, and evaluation of screening criteria

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Background/aim: The goal of this study was to investigate the incidence of retinopathy of prematurity (ROP) and the relationship between risk factors and disease in premature newborns in our neonatal intensive care unit.

Materials and methods: A total of 219 premature subjects were retrospectively evaluated for retinopathy. Demographic information, clinical data, and risk factors were reviewed.

Results: The gestational ages of the infants included in the study ranged between 25 and 36 weeks, and the birth weights ranged between 670 and 4460 g. In this study, the incidence of ROP was 20.1% (44) in preterm infants: 16 had stage 1 (36.4%), 15 had stage 2 (34.1%), 11 had stage 3 (25%), 1 had stage 4 (2.3%), 1 had stage 5 (2.3%), and 6 had plus (+) disease (7.2%). The risk factors associated with the development of ROP included low birth weight, ventilation treatment, bronchopulmonary dysplasia, and maternal preeclampsia. The risk factors were analyzed with logistic regression analysis. The odds ratios were 5.952 (95% confidence interval [CI]: 2.030–17.447), 20.070 (95% CI: 4.213–95.600), 5.879 (1.916–18.037), and 3.200 (95% CI: 1.002–11.535), respectively.

Conclusion: In this study, birth weight, ventilation treatment, bronchopulmonary dysplasia, and maternal preeclampsia were the most important risk factors for the development of ROP.

Key words: Retinopathy of prematurity, birth weight, preterm infants

1. Introduction

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy seen in premature infants, first described by Terry in 1942 (1); however, the etiology and pathogenesis of ROP remain unclear. It causes vision loss and blindness in newborns, but can be treated if detected appropriately and timely. Many risk factors are blamed for the development of ROP. The best known are low birth weight and low gestational age (GA). Multiple risk factors, including low birth weight, prematurity, oxygen therapy, blood transfusions, apnea, postnatal steroid treatment, and hypercapnia, contribute to the development of ROP (2,3). Oxygen therapy also plays an important role. A strong association exists between the severity of retinopathy and insulin-like growth factor 1 (IGF-1) in the early period following birth, and subsequent uncontrolled increase has been considered a risk factor (4,5). During the first stage of the pathogenesis of ROP, hyperoxia suppresses the activity of the vascular endothelial growth factor (VEGF) and alters the normal vascularization of the retina due to vasoconstriction and vasoobliteration of the existing immature vessels. In the second phase, upregulation of VEGF and other growth factors triggered by hypoxia induces vascular overproliferation. Thus, hypoxia and hyperoxia are involved in the pathogenesis of ROP (6). In more developed countries, ROP is primarily a concern for preterm births under 28 weeks of GA and 1000 g of weight, while severe ROP has been reported to develop in preterm births of up to 34 weeks of GA in developing countries (4). The incidence and risk factors of ROP have not been identified in Turkey. In this study, we compared the relevant literature data with the incidence of ROP and present risk factors in premature infants in our neonatal intensive care unit.

2. Materials and methods

Between February 2007 and January 2011, 219 premature subjects were retrospectively evaluated for retinopathy. Premature infants who were under 36 weeks of gestation age and who reached the 4th week after birth were included in the study. Premature infants who were born after 36 weeks of gestation and died in the first 4 weeks of life were

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excluded from the study. Birth weight (g); GA (weeks); activity, pulse, grimace response, appearance, respiration (APGAR) score; surfactant treatment; ventilator treatment; duration of oxygen therapy; development of intraventricular hemorrhage; presence of patent ductus arteriosus (PDA); development of bronchopulmonary dysplasia (BPD); frequency of blood transfusions; sepsis; and maternal risk factors including premature rupture of membranes, preeclampsia, and diabetes, were recorded.

2.1. Ophthalmological examination

Premature infants were first examined at 4 to 6 weeks after birth. The pupils of the subjects were dilated 1 h before the examination with three drops of 1% tropicamide and 2.5% phenylephrine 14 min apart. Fundus examination was performed with binocular indirect ophthalmoscope using a pediatric speculum, a sclera depressor, and a +20 diopter lens. Results were recorded according to the International Classification of Retinopathy of Prematurity (ICROP), which is based on the location of the disease in zones, the circumferential extent of the disease based on the clock hours, and the degree of vascularization stage (5). The eye examinations of the subjects were repeated after 1–2 weeks, depending on the findings. Subjects with stage 1 and stage 2 retinopathy were followed at our hospital, while subjects with stage 3 retinopathy and plus disease were followed at the Cerrahpaşa Faculty of Medicine, Department of Ophthalmology. Laser photocoagulation was performed on patients who had at least stage 3 disease. The other patients were followed up until retinal vascularization was complete.

2.2. Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software (USA) were used for statistical analysis of the results. In addition to definitive methods (mean, standard deviation, median, frequency, ratio), the Yates continuity correction, chi-square, Fisher's exact chi-square, Pearson's chi-square, and Mann–Whitney U tests were used to compare the data. Results were evaluated with 95% confidence intervals (CIs) and $P < 0.05$ was considered significant.

3. Results

The study was conducted on 219 premature infants born between February 2007 and January 2011. Retinopathy of prematurity (ROP) was found in 44 of the 219 infants included in the study (20.1%): 16 had stage 1 (36.4%), 15 had stage 2 (34.1%), 11 had stage 3 (25%), 1 had stage 4 (2.3%), 1 had stage 5 (2.3%), and 6 had plus disease (+) (7.2%). An overview of the general characteristics of the subject group is shown in Table 1. The mean gestational age of subject group was 32.81 ± 3.21 weeks, birth weight was 2041.48 ± 733.89 g, and sex distribution was 110 (50.2%) male and 18 (49.8%) female.

Neonatal and maternal risk factors for preterm birth were analyzed using Fisher's exact test and the Yates continuity correction test. The results are shown in Table 2.

Risk factors contributing to ROP, including premature rupture of membranes (PROM), surfactant treatment, APGAR score at the 1st minute, blood transfusions,

Table 1. Overview of general characteristics of the subject group.

		Min–Max	Mean ± SD
GA		25–36	32.81 ± 3.21
BW		670–4.460	2041.48 ± 733.89
		N	%
Sex	male	110	50.2
	female	109	49.8
GA	≤28	30	13.7
	29–32	54	24.7
	>32	135	61.6
BW	≤1000	18	8.2
	1000–1250	21	9.6
	1250–1500	21	9.6
	≥1500	159	72.6

N: number of patients (N = 219); GA: gestational age (weeks); BW: birth weight (grams).

Table 2. Univariate analysis of factors contributing to the development of ROP.

		ROP (+)	ROP (–)			
		N (%)	N (%)	P	Odds ratio	95% CI
[1]Sex	male	25 (22.7)	85 (77.3)	0.771	1.100	0.579–2.087
	female	23 (21.1)	86 (78.9)			
[2]GA	<32	38 (60.3)	25 (39.7)	0.001**	22.192	9.817–50.166
	≥32	10 (6.4)	146 (93.6)			
[2]BW	<1500	38 (63.3)	22 (36.7)	0.001**	25.736	11.244–58.905
	≥1500	10 (6.3)	149 (93.7)			
[2]OT	P	46 (26.9)	125 (73.1)	0.002**	8.464	1.975–36.282
	N	2 (4.2)	46 (95.8)			
[2]PDA	P	5 (71.4)	2 (28.6)	0.006**	9.826	1.843–52.386
	N	43 (20.3)	169 (79.7)			
[2]RDS	P	32 (60.4)	21 (39.6)	0.001**	14.286	6.720–30.367
	N	16 (9.6)	150 (90.4)			
[2]VT	P	41 (61.2)	26 (38.8)	0.001**	32.665	13.231–80.642
	N	7 (4.6)	145 (95.4)			
[2]AS	P	9 (28.1)	23 (71.9)	0.492	1.485	1.485–3.466
	N	39 (20.9)	148 (79.1)			
[2]BPD	P	31 (75.6)	10 (24.4)	0.001**	29.359	12.293–70.117
	N	17 (9.6)	161 (90.4)			
[2]Sepsis	P	17 (43.6)	22 (56.4)	0.001**	3.714	1.769–7.799
	N	31 (17.2)	149 (82.8)			
[2]MP	P	13 (41.9)	18 (58.1)	0.012*	2.791	1.331–6.635
	N	35 (19.6)	144 (80.4)			
[2]IVH	P	9 (52.9)	8 (47.1)	0.004**	4.702	1.705–12.967
	N	39 (19.3)	163 (80.7)			
[2]BT	P	29 (74.4)	10 (25.6)	0.001**	24.575	10.380–58.175
	N	19 (10.6)	161 (89.4)			

BW: birth weight (grams); GA: gestational age (weeks); P: positive; N: negative; OT: oxygen therapy; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome; VT: ventilator treatment; AS: asphyxia; BPD: bronchopulmonary dysplasia; MP: maternal preeclampsia; IVH: intraventricular hemorrhage; BT: blood transfusion; N: number of patients.
[1]Chi-square test, [2]continuity correction (Yates) test, *P < 0.05, **P < 0.01.

respiratory distress syndrome (RDS), birth weight, BPD, and maternal preeclampsia were evaluated with stepwise logistic regression analysis. The results are shown in Table 3. The model was significant at the 10th step, and the expressiveness coefficient was good (78.3%).

4. Discussion

The frequency of ROP was 20.1% in this study. Univariate and multivariate logistic regression tests revealed that birth weight, ventilation therapy, bronchopulmonary dysplasia, and maternal preeclampsia were the most important risk factors in the development of ROP. Different from

Table 3. Analysis of factors contributing to the development of ROP with logistic regression.

	B	SE	P	Exp (B)	95% CI
BW < 1500 g	1.784	0.549	0.001**	5.952	2.030–17.447
RDS	–1.282	0.794	0.107	0.276	0.059–1.316
VT	2.999	0.796	0.001**	20.070	4.213–95.600
BPD	1.771	0.572	0.002**	5.879	1.916–18.037
MP	1.163	0.654	0.045*	3.200	1.002–11.535

BW: birth weight (grams); RDS: respiratory distress syndrome; VT: ventilator treatment; BPD: bronchopulmonary dysplasia; MP: maternal preeclampsia. *P < 0.05, **P < 0.01.

other previously published studies, we identified that the duration of ventilation treatment did not affect the severity of ROP. Recently, the survival rates of neonates with very low birth weight and GA have rapidly increased parallel to the advances in assisted reproductive technologies and neonatology. As a result, there has been an increase in the incidence of ROP over the years (6). Retinopathy is one of the most important problems in risky preterm births and can lead to visual impairments and potentially to blindness. However, ROP can be prevented with appropriate and early detection and treatment. Therefore, knowing the causes and risk factors of ROP is crucial for preventing the disease.

A wide range of ROP incidence (23%–56.2%) has been reported in Turkey (7–9). The frequency was slightly lower in our study. In this study, the frequency of ROP was 9.1% in infants who weighed more than 2000 g, and 13.6% in infants over 32 weeks of GA. We detected 4 patients with stage 3 ROP whose birth weeks were over 33 weeks, and all required surgical treatment. Akman et al. also detected 11 infants with ROP who required surgical treatment and whose GA was between 32 and 34 weeks (10). Another study conducted in Turkey demonstrated that the frequency of ROP was 56% in infants with 32–35 weeks of GA. Similar findings were shown in studies from Saudi Arabia, Vietnam, India, and China, and in Turkey, with recommendations to include more mature infants in screening programs to avoid missing cases (7,11,12).

In this study, the risk of ROP development was 32.7 times higher in infants who received ventilation treatment using univariate testing (Table 2). In addition, the odds ratio was 20.1 in logistic regression analysis. Therefore, we found that mechanical ventilation treatment was the most important risk factor in ROP development. Various studies have reported that ventilator treatment increases the development of ROP (13–15). However, the effect of ventilator treatment is markedly larger in our study. Mechanic ventilation delivers oxygen to the lungs with positive pressure, and a longer exposure to high oxygen pressure may contribute to ROP development. Recently, Giannantonio et al. published findings on ROP risk factors and noted that prolonged mechanical ventilation was also associated with ROP requiring treatment (14). Fortes Fillo et al. found that mechanical ventilation was a significant risk factor only for the development of ROP in infants with a GA of 32 weeks or greater (15). The researchers concluded that although infants with a lower GA are challenged with consequences of general immaturity, larger infants with higher GA tend to be sicker with more comorbidity. We found that the number of infants under 32 weeks (84) was much lower than the number of infants over 32 weeks (135), and ventilation treatment was the most important factor contributing to the development of ROP. These findings supported the results of their study.

In our study, the risk of developing ROP was 29.4 times higher in infants with bronchopulmonary dysplasia using univariate testing (Table 2). In addition, the odds ratio for the presence of bronchopulmonary dysplasia was 5.9 in logistic regression analysis (Table 3). Holmström et al. found that the presence of bronchopulmonary dysplasia was the most powerful risk factor in the development of ROP (16). Giapros et al. showed the synergistic effect of low GA and chronic pulmonary disease on the development of ROP (17). In our study, patients with bronchopulmonary dysplasia had a birth weight of less than 1000 g, received postnatal steroids, and were under long-term ventilator and oxygen therapy. Therefore, other risk factors may have synergistic effects. Zamorano Jimenez et al. observed that postnatal steroid treatment was a risk factor for the development of ROP (18). Similarly, Shah et al. showed that chronic pulmonary disease was a risk factor for ROP that required surgery (13).

Low birth weight and short GA have been confirmed as the key risk factors for the development of ROP (16,19). Our study and other studies conducted in Turkey have demonstrated that birth weight was more important than GA as a risk factor in the development of ROP (20,21) (Figures 1 and 2).

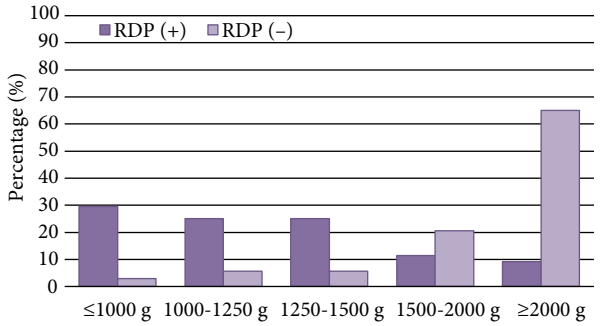

Figure 1. Distribution of ROP according to birth weight.

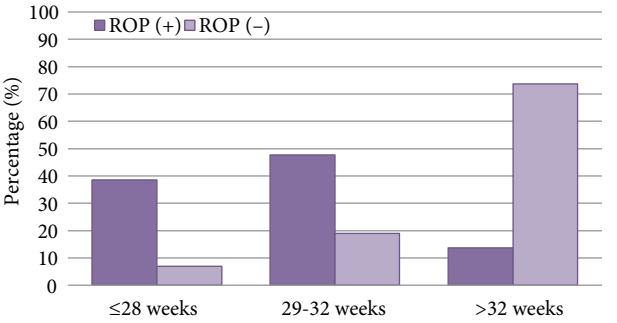

Figure 2. Distribution of ROP according to GA.

Several studies conducted in Turkey and throughout the world revealed that maternal preeclampsia played an important role in the development of ROP (13,16,18,22,23). Similarly, we found that the odds ratio for maternal preeclampsia was 3.2 using logistic regression tests (Table 3). In addition, the presence of preeclampsia in mothers of 4 infants with ≥2000 g birth weight and ROP (+) is remarkable. Although the exact mechanism of ROP in infants born to preeclamptic mothers is not known, retinal hypoxia, altered maternal angiogenic factors, inflammation, and oxidative stress might contribute to this multifactorial morbidity.

Other risk factors that contribute to the development of ROP include sepsis, RDS, hypercapnia, acidosis, anemia, intraventricular hemorrhage, blood transfusions, multiple pregnancy, and neonate APGAR score. However, the question of which factor independently causes retinopathy is unanswered (20,23,24). Multiple risk factors may be present in the same infant. In our study, we found that blood transfusion, sepsis, PROM, PDA, IVF, and an APGAR score of 7 or lower contributed to the risk, while intraventricular hemorrhage, maternal diabetes, and neonatal convulsions did not.

Although ROP is predominantly reported in infants below 28 weeks of GA and 1000 g of birth weight in developed countries, in developing countries severe ROP may develop in up to 34-week preterm babies (25,26). In addition, the presence of severe ROP that required surgery in 4 subjects with birth weights higher than 1500 g and GA older than 33 weeks further showed the need for follow-up for retinopathy in all preterm infants.

According to the last declaration of the American Academy of Ophthalmology, the American Academy of Pediatrics, and the American Association for Pediatric Ophthalmology and Strabismus, all babies below 1500 g of birth weight or 32 weeks of GA must be screened for ROP; moreover, infants with birth weights of 1500–2000 g or with more than 32 weeks of GA who have some risk factors for ROP formation should be screened (27). Although individual guidelines exist for each neonatal intensive care unit, as in most developed countries, there are no evidence-based national screening guidelines in Turkey. The increasing number of studies conducted in Turkey has shown that national guidelines are needed, and older infants should undergo screening (28).

In conclusion, we found that low birth weight (specifically below 1000 g), bronchopulmonary dysplasia, maternal preeclampsia, and ventilation treatment were the most common risk factors for the development of ROP. Our study mainly consisted of infants who were over 32 weeks of GA and 1500 g of weight. Thus, we shed light on the risk factors for developing ROP. To prevent irreversible visual loss, the population at risk should be better identified, risk factors should be recognized, and appropriate screening criteria should be adopted. Until those criteria are established, caution should be taken, and wider screening criteria than those used in developed countries should be applied.

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