Evaluation of Risk Factors Affecting Development of Retinopathy in Premature Infants

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Cite this article as: Gül F, Bülbül A. Evaluation of Risk Factors Affecting Development of Retinopathy in Premature Infants. JAREM 2018; 8(3): 171-6.

ABSTRACT

Objective: We aimed to investigate the prevalence, risk factors, and prognosis of retinopathy of prematurity in premature infants.

Methods: Between January 1, 2008 and December 31, 2012 we included 537 premature infants born at the 34th gestational week and previously treated at the Neonatal Intensive Care Unit of our hospital. Risk factors for the development of retinopathy of prematurity were retrospectively reviewed.

Results: Our study included 290 female and 247 male infants; 90 of these infants (16.7%) were at different stages of retinopathy of prematurity. Of these, 55 (61.1%) had stage 1, 24 (26.7%) had stage 2, 9 (10%) had stage 3, and 1 (1.11%) had stage 5 retinopathy of prematurity. Spontaneous regression was observed in 77 patients; laserphotocoagulation surgery was performed in 13 patients, and anti-VEGF therapy was given to 2 patients. One patient developed total retinal detachment. Birth weight, gestational weeks, Apgarscore (1st and 5th minutes), oxygen treatment duration, surfactant treatment, ventilator treatment and duration, maximum FIO₂, anemia, transfusion, sepsis, apnea, intraventricular hemorrhage, Bronchopulmonary Dysplasia (BPD) other diseases (NEC, phototherapy, and PDA), antenatal steroid treatment, hospitalisation duration were significantly higher in patients with premature retinopathy; however, no significant difference was seen in sex, race, and maternal preeclampsia in these patients.

Conclusion: We found a lower incidence of premature retinopathy in our study than in other studies in the literature. The majority of our patients with retinopathy of prematurity required early mechanical ventilation and oxygen supplementation. A good understanding of the risk factors for the development of premature retinopathy and risk factors in premature infants and early diagnosis and treatment are very important for the prevention of blindness.

Keywords: Retinopathy of prematurity, risk factors, premature infants

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease caused by the fibrovascular proliferation of the immature retinal vessels of premature infants (1). ROP is one of the leading causes of preventable blindness in childhood (2).

Low birth weight infants are provided to survive with improvements in neonatal intensive care conditions, but this results in more infants with ROP (2). ROP is the second most common cause of blindness in newborns in the United States. In the United States, approximately 500 newborns lose their vision every year due to ROP, and 2300 of them have various visual problems (3, 4). It is estimated that 6%-18% of childhood blindness is related to ROP in developed countries (5). The World Health Organization, in its vision 2020 program, included ROP disease as a public health problem among the priority preventable diseases (6).

Retinopathy of prematurity (ROP) is usually seen in infants with low birth weight. It was first called as "retrolental fibroplasia" in 1942 when premature infants were diagnosed with fibroblastic mass behind the lens (7). In the etiology of ROP, there is local retinal ischemia in the acute phase and the resulting neovascularization; there is membrane formation in the chronic phase, and then, retinal detachment can be seen (8). The incidence of ROP increases inversely with small gestational age and low birth weight.

For screening ROP, the American Academy of Pediatrics, American Association of Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology recommend ROP screening to all premature infants born <1500 g, <30 weeks of gestation, or unstable 1500–2000 g birth weight infants at risk of ROP (9). Screening for ROP is recommended on postconcep-

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This study was presented in 1st Friends of Children and Neonatal Congress, April 20, 2013, İstanbul, Turkey.

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Received Date: 02.04.2018 Accepted Date: 26.04.2018

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DOI: 10.5152/jarem.2018.2084

tional week 31 for babies with <27 weeks of gestation and on postconceptional week 4 for premature infants with >27 weeks of gestation (10).

The aim of the present study was to determine the effective risk factors in the etiology for ROP development and the incidence of ROP and to evaluate the prognosis with treatment modalities in premature infants in our neonatal intensive care unit.

METHODS

Study group

All infants who were treated at the neonatal intensive care unit of our hospital between January 1, 2008 and December 31, 2012, whose gestational period was ≤ 34 weeks, and who were examined for retinopathy were included in our study. Infants who had lost their lives prior to the retinopathy examination, who were transferred to different hospitals for various reasons, or who were not followed up due to being on postconceptional week 52 were excluded from the study.

Study Data

The antenatal, natal, and postnatal features and demographic data of the infants were collected retrospectively from patient files in accordance with the Declaration of Helsinki. Respiratory therapy models and characteristics (oxygen uptake time, highest FiO_2 value, mechanical ventilation models and durations, and surfactant application) applied to all infants, follow-up diagnoses of infants, frequency of blood transfusions due to patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, bronchopulmonary dysplasia (BPD), and anemia were recorded.

Table 1. Distribution of general characteristics of all infants included in the study

Demographic characteristics	n=537
Birth weight, g*	1704 $\pm$ 509
Gestational age, week*	31.7 $\pm$ 2.7
Apgar score	
1 min	6.04 $\pm$ 1.41
5 min	8.21 $\pm$ 1.09
Gender, n (%)	
Female	290 (54%)
Male	247 (46%)
Antenatal steroid administration, n (%)	159 (29.6)
ROP, n (%)	90 (16.8)
Multiple pregnancies, n (%)	58 (12.1)
Mortality, n (%)	42 (7.8)

*Values are expressed as mean $\pm$ standard deviation

ROP Examination

The first examinations of premature infants were performed in the newborn unit at 4–6 weeks after birth or on postconceptional weeks 31–33. Patients who were discharged before the first examination were checked at the ROP polyclinic of the ophthalmology clinic. All infants diagnosed with ROP were followed up until postconceptional week 52. Results were recorded according to the international ROP classification (11).

Statistical Analysis

To determine the risk factors for development of ROP independently using stratified sampling, a case–control cross-sectional control group with the same gestational age, the same mean birth weight, and the same number was established among the patients. In this way, it was aimed to determine the risk factors that may affect ROP development without the effects of gestational week and birth weight.

Data were analyzed by using the Statistical Package for the Social Sciences version 21.0 program (IBM Corp., Armonk, NY, USA). Data were expressed as mean $\pm$ standard deviation, percentage (%), and median (minimum–maximum). Kolmogorov-Smirnov test was used to determine the distribution of variables. Mann-Whitney U test and independent sample t-test were used to analyze quantitative data. Fisher's exact test was used to analyze qualitative data when chi-square test/chi-square conditions could not be provided. A p value <0.05 was accepted as statistically significant.

RESULTS

A total of 636 infants with a gestational age of ≤ 34 weeks were born in our hospital during the study period. Of the 636 patients, 36 who were referred to different hospitals for various reasons during the study, 42 who died prior to the examination of ROP, and 21 who were not followed up after discharge were excluded from the study. Overall, 537 infants were included in the study. The mean gestational age of the infants was 31.7 $\pm$ 2.7 weeks, and 54% (n=290) were girls. On ROP examination, retinopathy at various stages was detected in 90 (16.7%) infants. Of the 90 infants, 56 (62.3%) had stage I, 24 (26.6%) had stage II, 9 (10%) had stage III, and 1 (1.1%) had stage V disease. The prenatal and natal characteristics of the subjects are shown in Table 1. The distribution

Table 2. Distribution of infants with ROP according to the stages within the total patient distribution

	No. of patients with ROP, n	Ratio to total patient (n:537), %
Stage I	56	10.4
Stage II	24	4.5
Stage III	9	1.7
Stages IV and V	1	0.1
Total	90	16.7

ROP: retinopathy of prematurity

of infants with ROP according to the stages in the total patient distribution is shown in Table 2.

The mean gestational age of the patients with ROP was 28.3 ± 2.6 (23–34) weeks, and mean birth weight was 1148 ± 335 (570–2100) g. It was determined that as birth weight and gestational age increased, the incidence of ROP decreased significantly ($p=0.00$). There were significant differences with regard to birth weight, gestational week, 1 and 5 min Apgar scores, and antenatal steroid administration rates among infants with and without ROP (Table 3). There was no significant difference between the groups with and without ROP with regard to oxygen therapy demand,

which was one of the risk factors included in the study ($p=0.22$). However, duration of oxygen treatment, maximum FiO_2 , requirement and duration of ventilator treatment, requirement of surfactant treatment, erythrocyte transfusion requirement, sepsis, apnea, IVH, BPD, NEC, phototherapy requirement, antenatal steroid administration, and hospital stay were significantly higher in patients with ROP (Table 3). It was observed that the presence of preeclampsia in mothers and gender did not make a significant difference in patients with ROP. In our study, 78.9% of patients with ROP were transfused (26.7% before the examination, 16.7% after the examination, and 35.6% before and after the examination). The rate of transfusion was significantly higher in patients with ROP than in those without ROP (Table 3).

Among our cases, a case–control group consisting of 90 premature infants with the same mean gestational week and birth weight was determined using stratified sample. Thus, it was

Table 3. Comparison of prenatal, natal, and postnatal features and risk factors between the groups with and without ROP

Risk factors	ROP (+) n=90	ROP (-) n=447	p
Birth weight, g	1148±335	1816±463	0.00
Gestational age, week	28.3±2.6	32.3±2.1	0.00
Gender, male, n (%)	39 (43.3)	208 (46.5)	0.57
Apgar score			
1 min	5.12±1.5	6.23±1.3	0.00
5 min	7.40±1.1	8.37±1.0	0.00
Antenatal steroid treatment rates, n (%)	46 (51.1%)	113 (25.3%)	0.00
Preeclampsia in mother, n (%)	22 (24.4)	72 (16.1)	0.058
O ₂ therapy demand, n (%)	90 (100)	436 (97.5)	0.22
O ₂ therapy duration, day	35.3±56.3	5.9±9.2	0.00
Maximum FiO_2 value	55.7±13.9	40.5±12.6	0.00
Mechanical ventilator therapy demand, n (%)	85 (94.4)	276 (61.7)	0.00
Mechanical ventilator duration, day	19.9±49.2	3.1±5.4	0.00
Surfactant therapy demand, n (%)	63 (70)	113 (25.3)	0.00
Erythrocyte transfusion demand, n (%)	71(78.9)	98 (21.9)	0.00
Anemia diagnosis, n (%)	79 (87.8)	163 (36.5)	0.00
Proven sepsis diagnosis, n (%)	33 (36.7)	68 (15.2)	0.00
IVH (stages III and IV), n (%)	40 (44.4)	51 (11.4)	0.00
BPD, n (%)	37 (41.1)	17 (3.8)	0.00
PDA, n (%)	12 (13.3)	14 (3.1)	0.08
Phototherapy treatment, n (%)	74 (82.2)	294 (65.7)	0.00
NEC, n (%)	18 (20)	46 (10.3)	0.00

ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis

Table 4. Comparison of perinatal and clinical risk factors in patients with ROP and with the control group constituted with stratified sampling

Demographic characteristics	ROP (+) n=90	Control group n=90	p
Gender, male, n (%)	39 (43.3)	47 (52.2)	0.23
Birth weight, g	1148±335	1225±219	0.07
Gestational age, week	28.3±2.6	28.9±1.4	0.07
Apgar score			
1 min	5.12±1.5	5.59±1.3	0.05
5 min	7.40±1.1	7.80±1.1	0.01
Risk factors			
Preeclampsia in mother, n (%)	22 (24.4)	23 (25.6)	0.86
O ₂ therapy rate, n (%)	90 (100)	88 (97.8)	0.49
O ₂ therapy duration, day	35.3±56.3	14.2±15.4	0.00
Maximum FiO_2	55.7±13.9	49.8±13.3	0.06
Mechanical ventilator therapy rate, n (%)	85 (94.4)	80 (88.9)	0.17
Mechanical ventilator duration, day	19.9±49.2	8±8.9	0.00
Erythrocyte transfusion demand, n (%)	71 (78.9)	58 (64.4)	0.03
Anemia diagnosis frequency, n (%)	79 (87.8)	72 (80)	0.15
Clinical sepsis diagnosis, n (%)	33 (36.7)	27 (30)	0.26
IVH (stages III and IV), n (%)	40 (44.4)	25 (27.8)	0.02
BPD, n (%)	37 (41.1)	14 (15.6)	0.00
Hospitalization duration, day	70.7±51.4	48±21.9	0.00

ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia

aimed to determine the risk factors that may affect ROP development without the effect of the main risk factors, gestational week, and birth weight. The results of the comparison of the demographic characteristics of mothers and infants between the two groups are presented in Table 3. When the factors affecting ROP development were compared between the two groups, there was a significant difference with regard to the duration of oxygen therapy, duration of mechanical ventilation, presence of transfusion, and presence of IVH. In the group with ROP, 5 min Apgar score, antenatal steroid administration, duration of oxygen treatment, maximum FiO_2 , duration of ventilator therapy, IVH, BPD, and hospital stay were significantly higher (Table 4).

In the follow-up of infants with ROP, in 77 of the 90 infants, ROP findings completely regressed without needing any intervention, 13 underwent laser photocoagulation, two received anti-vascular endothelial growth factor (bevacizumab) additionally, and one had visual loss due to total retinal detachment.

DISCUSSION

Retinopathy of prematurity (ROP) is one of the leading causes of preventable blindness in childhood worldwide (11). Nowadays, with the development of neonatology and current approaches, extremely low birth weight premature infants' survival rates increased, but this resulted in an increase in morbidities that may be observed in the long term, such as ROP.

Many risk factors for formation of ROP have been studied since the beginning of the 1940s. It was found that the most important risk factors in ROP development are low birth weight and gestational age of the infant (12). Other identified risk factors include oxygen toxicity, low Apgar score, mechanical ventilation support, blood transfusion, acidosis, apnea, IVH, NEC, PDA, sepsis, and multiple pregnancies (11).

Different results have been reported with regard to the frequency of ROP. It has been reported in the literature that the incidence of ROP is approximately 16%-65.8% (13-15). In our country, the frequency of ROP in different studies varies between centers, and it is reported to be seen in 15.4%-36.3% (7, 16-20). In the CRYO-ROP study of 4099 premature infants from 23 centers, the prevalence of ROP in infants born <1251 g was 65.8% and 81.6% in infants <1000 g (10). In the study conducted in our country between 1992 and 2005 with 465 premature infants, the total prevalence of ROP was found to be 30.3%; when evaluated according to gestational week, it was reported to be 70% at ≤ 28 weeks, 32% at 29-32 weeks, and 15.5% at ≥ 32 weeks (19). In a multicenter TR-ROP study of 6115 infants, the incidence of ROP was found to be 27%, and the incidence of severe ROP ($\geq$ stage III) was found to be 6.7% (21). In our study, the frequency of ROP in all stages was determined as 16.7%, and this value was found to be in the lower limit of the reported values. This was thought to be due to two reasons: protocols applied in our hospital, especially in the use of oxygen and non-invasive ventilation strategies in infants with mechanical ventilation, and the mean birth weight and gestational age in our study were higher than the reported studies.

Although many risk factors have been defined for ROP, the most important risk factors have been shown to be gestational week and low birth weight (22, 23). In our study, the mean birth weight of patients with ROP was found to be significantly lower than those without ROP. Our results support this information. Palmer et al. (13), in their study of 4099 infants with birth weight ≤ 1250 g, reported that while the rate of ROP in infants <750 g is 90%, it decreases to 10% in infants >1500 g. However, there are significant differences in the distribution of ROP incidence according to gestational weeks. In our study, mean gestational week was found to be significantly lower in patients with ROP.

Several studies have been conducted to determine the effect of oxygen therapy on ROP, and high oxygen therapy has been reported to increase the frequency and severity of ROP in most of them. In our study, in accordance with the general findings in the literature, the duration of oxygen therapy in infants with ROP was found to be significantly longer than those without ROP. Yalaz et al. (24) reported a significant relationship between ROP development and prolonged oxygen treatment time. Patz reported ROP development in infants who received low level of oxygen ($\text{FiO}_2=40\%$) to be 6% and high level of oxygen ($\text{FiO}_2=65\%-70\%$) to be 60% (25). In our study, it was found that the maximum FiO_2 level in the ROP group was significantly higher than that in the group without ROP. An important cause of ROP development in infants weighing >1500 g or with higher gestational weeks may be uncontrolled oxygen therapy administered in the incubator. When oxygen saturation as measured by pulse oximetry is >85%-90% due to fetal hemoglobin elevation in premature infants, the oxygen concentration in the blood is not known very precisely. Therefore, it is stated in the literature that maintaining oxygen saturation in premature infants <90% may be protective for ROP (26).

Patent ductus arteriosus (PDA) relationship with ROP has been studied in many studies. Chen et al. (27) found that there is a two-fold higher risk for ROP in patients with PDA and band ligation, whereas Wani et al. (28) found that PDA does not constitute a statistically significant risk in the development of ROP. In our study, more PDA was detected in the ROP group.

Necrotizing enterocolitis (NEC) is a disease caused by immaturity similar to ROP. Many studies have investigated whether there is a significant relationship between ROP and NEC. In our study, we found that the rates of NEC in patients with ROP were higher than those without ROP. Wani et al. (28) found the frequency of NEC to be a statistically significant risk factor for ROP, whereas Chen et al. (27) stated no significant relationship between ROP and NEC.

It is known that the frequency of blood transfusion demand in premature infants is related to ROP development (18-20). Since oxygen bonding of erythrocytes in adults is lower than those in premature infants, there is an increase in the amount of oxygen offered to the tissues by transfusion, resulting in inappropriate hyperoxia in the tissues and contributing to the development of ROP. Our study also supports the knowledge that transfusion poses a risk for ROP development, as reported in the TR-ROP study (21).

Another risk factor that may affect the incidence of ROP in premature newborn is sepsis, which is a multisystem disease. It has been thought that it may cause the release of proinflammatory cytokines, may cause damage to the newly developing vessels in the retina, and may cause severe ROP through angiogenic agents. Chen et al. (27) had shown that sepsis increases the frequency of ROP by 4.5-fold in preterm infants with >27 gestational weeks. Wani et al. (28) reported that both bacterial and fungal sepsis increase the risk of ROP. In our country, Yalaz et al. (24) and Kavurt et al. (18) found in their studies that sepsis increases ROP frequency. In our study, we found that the rates of proven sepsis in blood culture were significantly higher in patients with ROP.

CONCLUSION

We found that the frequency of ROP development was lower in our study than in reported studies. When the main risk factors in ROP development, gestational week, and birth weight were excluded, NEC, IVH, BPD, proven sepsis, blood transfusion frequency, and oxygen and mechanical ventilation duration were determined to be important risk factors in ROP development. All interventions to reduce risk factors that are effective in ROP development will reduce the frequency of ROP development. Knowing the risk factors for ROP development well and the early diagnosis and treatment of all premature infants with risk factors will decrease the incidence of vision loss that is an important morbidity.

Data were collected retrospectively using the file research information form in accordance with the Declaration of Helsinki. Therefore, informed consent was not obtained.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Informed consent was not taken from patients due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.G., A.B.; Design - F.G., A.B.; Supervision - F.G., A.B.; Resources - F.G.; Materials - F.G.; Data Collection and/or Processing - F.G.; Analysis and/or Interpretation - F.G., A.B.; Literature Search - F.G.; Writing Manuscript - F.G.; Critical Review - A.B.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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