The Risk Factors for Retinopathy of Prematurity and Need of Laser Photocoagulation: A Single Center Experience

Prematüre Retinopatisi Gelişimi ve Lazer Fotokoagülasyon Gereksinimi için Risk Faktörleri: Tek Merkez Deneyimi

Emrah Utku Kabataş[1], Serdar Beken[2], Banu Aydın[2], Dilek Dilli[3], Ayşegül Zenciroğlu[3], Nurullah Okumuş[3]

[1]Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ophtalmology Unit, Ankara, Turkey
[2]Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Neonatology Unit, Ankara, Turkey
[3]Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Neonatology Unit, Ankara, Turkey

ABSTRACT

Objective: It was aimed to determine the risk factors for the development of retinopathy of prematurity (ROP) in premature infants. The factors affecting the need of laser photocoagulation (LP) were also investigated.

Methods: The study was prospectively conducted at a tertiary neonatal intensive care unit (NICU) between March 2011 and August 2012. A total of 113 premature infants born at <37 weeks of gestational age were evaluated. The patients were divided into two groups according to ROP development; Group 1: with ROP and Group 2: without ROP.

Results: In Group 1 (n=53), 15 patients (38.3%) had stage >2 ROP. LP was performed on 18 (33.9%) patients. While the mean birth weight and gestational age were lower, the rates of associated disorders, use of prophylactic or therapeutic caffeine for apnea, and need of red blood cell transfusion were higher in Group 1 compared to Group 2 (p<0.05). Multivariate analysis showed that the need of transfusion in the first 10 days of life has increased the risk for ROP (OR: 1.9, 95% CI: 1.1-3.3, p=0.01). In another model, it was determined that the higher gestational age and the absence of apnea or prophylactic caffeine use were associated with reduced need of LP [OR: 0.5, 95% CI: 0.2-0.9), p=0.02, and (OR: 0.1, 95% CI: 0.03-0.9), p=0.02), respectively].

Conclusion: Red blood cell transfusion in early neonatal period may contribute to the development of ROP. The use of prophylactic or therapeutic caffeine for apnea could negatively affect the progression of ROP with need of LP.

Key Words: Retinopathy of prematurity, risk factors, transfusion, caffeine

ÖZET

Giriş: Bu çalışmada kliniğimizde takip edilen prematüre bebeklerde Prematüre Retinopatisi (ROP) gelişmesini etkileyen faktörlerin belirlenmesi ve lazer fotokoagülasyon (LF) yapılan bebeklerde risklerin tanımlanması amaçlanmıştır.

Yöntemler: Mart 2011-Ağustos 2012 tarihlerinde Dr. Sami Ulus Kadın Doğum, Çocuk Eğitim ve Araştırma Hastanesi Yenidoğan Yoğun Bakım Kliniğinde 37 haftanın altında doğan ve göz muayeneleri yapılan 113 prematüre bebeğin kayıtları prospektif olarak incelendi. Hastalar, ROP gelişen (Grup 1, n=53) ve gelişmeyen (Grup 2, n=60) olmak üzere iki gruba ayrıldı. Demografik ve klinik veriler kaydedildi. Çalışma parametreleri ROP gelişimi ve LP tedavisi ihtiyacı açısından değerlendirildi.

Bulgular: Grup 1'de 15 hasta (38.3%) Evre>2 ROP olarak değerlendirildi. Toplam 18 hastaya (33.9%) (Evre 3, plus hastalık ve agresif ROP) LF yapıldı. Doğum ağırlığı ve gestasyonel yaş Grup 1'de daha düşükken (p<0.05); kafein kullanımı, eritrosit transfüzyonu daha fazla olarak bulundu (p<0.05). Multivaryans analiz ile değerlendirildiğinde ilk 10 gün içinde eritrosit transfüzyonu alma ROP gelişme riskini arttırırken (OR: 1.9, 95% CI: 1.1-3.3, p=0.01); yüksek gebelik haftası, profilaktik/terapötik kafein tedavisinin verilmemesinin LF ihtiyacını azalttığı saptanmıştır [OR: 0.5, 95% CI: 0.2-0.9), p=0.02, and (OR: 0.1, 95% CI: 0.03-0.9), p=0.02)].

Sonuç: Hayatın erken dönemlerinde eritrosit transfüzyonu ROP gelişme riskine katkıda bulunabilir. Prematüre retinopatisi gelişen hastalarda ise profilaktik/terapötik kafein kullanımı LF riskini arttırabilir. Bu nedenlerle prematüre bebeklere eritrosit transfüzyonu verilirken ve kafein tedavisi başlarken dikkatli olunmalıdır.

Anahtar Sözcükler: Prematüre retinopatisi, risk faktörleri, transfüzyon, kafein

Address for Correspondence / Yazışma Adresi: Emrah Utku Kabataş M.D, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Babür Street, No:44, Altındağ, Ankara, Turkey, Phone: +90 505 213 64 14 Fax: + 90 312 317 03 53 Email: dremrahutku@yahoo.com

INTRODUCTION

Retinopathy of prematurity (ROP) is a preventable cause of blindness. It was first described in 1942 by Terry et al. (1). The incidence of ROP has been on the rise due to the increasing number of viable premature infants in neonatal intensive care units (NICU). The most important risk factors leading to the development of ROP are the infant's gestational age, birth weight and immaturity (2). Although the infants with a gestational age of <32 weeks and birth weight of <1500 g appear to be at high risk for ROP, it may also occur in infants older than 32 weeks and above 1500 g (3). The studies conducted on etiopathogenesis of ROP showed that beside prematurity, other risk factors such as light exposure, blood transfusion, metabolic acidosis-alkalosis, sepsis, methylxanthine therapy, vitamin E-selenium-copper-magnesium deficiency, beta-blocker use, respiratory distress syndrome (RDS), pneumothorax, mechanical ventilation treatment, oxygen therapy, hypercarbia, perinatal asphyxia, patent ductus arteriosus (PDA), intracranial hemorrhage (ICH), necrotizing enterocolitis (NEC), chronic lung disease (CLD), renal failure, prolonged total parenteral nutrition (TPN), maternal bleeding, preeclampsia, chorioamnionitis, and *in vitro* fertilization play important roles in the development of ROP (4-6). However, it is difficult to identify the main risk factors that contribute to the development of ROP since most of these conditions are already present in infants with serious systemic illness.

Nowadays, the most frequently used treatment types for ROP are close follow-up and laser photocoagulation (LP). There are few studies identifying the risk factors that affect the progression of ROP stage and need of LP in infants (7,8). Therefore, in this study, it was aimed to evaluate the main risk factors affecting the development of ROP in premature infants, as well as the need for LP treatment.

METHODS

The study was conducted as a prospective study at the tertiary neonatal intensive care unit (NICU) of Dr. Sami Ulus Maternity and Children Training and Research Hospital between March 2011-August 2012. During the study period a total of 2508 patients were followed up in NICU. Among them, 378 patients were at a gestational age of <37 weeks. Our inclusion criteria included all premature infants with a gestational age of <32 weeks, a birth weight of <1500 g, and premature infants with a gestational age between 32-37 weeks, needed of prolonged mechanical ventilation and having associated disorders such as anemia, apnea, RDS, PDA, ICH, NEC, CLD, perinatal asphyxia, and sepsis. Our exclusion criteria included the infants with a gestational age of ≥37 weeks and infants with severe congenital anomalies.

A total of 113 preterm infants who satisfied the study criteria were evaluated. The initial ROP examinations were performed when corrected age was 31 weeks in infants with gestational age of ≤27 weeks, while the infants born at or beyond 28 weeks were examined by the postnatal fourth to fifth week. All fundus examinations were performed by the same ophthalmologist (first author). Pupil dilation was ensured by administering a mydriatic combination of 2.5% phenylephrine HCl and 0.5% tropicamide, instilled one drop each in 2 to 3 doses, each five minutes apart, 1 hour prior to examination. Topical anesthesia was provided with 0.5% proparacaine HCl drops. A drop of 0.5% proparacaine was used for topical anesthesia. The fundus was examined with a binocular indirect ophthalmoscope and +28.0 dioptry lens, lid speculum, and scleral depressor approximately one hour, after the first instillation.

In all cases, the stages of ROP, location, and the extent of spread of the disease were classified according to the recommendations of International Committee for the Classification of Retinopathy of Prematurity (9).

The follow-up examinations were performed once a fortnight in patients with low-risk pre-threshold disease, and at least once a week for ones with high-risk pre-threshold disease. Infants with normal vascularization of the retina to the ora serrata were not re-examined.

The patients were treated with indirect ophthalmoscopic argon LP [OcuLight GL (532 nm) Laser Photo-coagulator] of the entire avascular retina with near confluent burns when type 1 ROP developed, as determined by the *Early Treatment for Retinopathy of Prematurity* (ETROP) study (10).

The patients were divided into two main groups according to development of ROP:

- *Group 1: patients with ROP*
- *Group 2: patients without ROP*

The patients with ROP were divided two subgroups according to need of LP:

- *Group 1a: ROP with LP*
- *Group 1b: ROP without LP*

Demographic and clinical data including the patients' gender, gestational age, birth weight, the presence of associated disorders such as RDS with prophylactic or therapeutic use of surfactant, significant PDA with ibuprofen use, indirect hyperbilirubinemia (IHB) requiring phototherapy, ICH (grade ≥2), apnea with prophylactic or therapeutic use of caffeine, hypotension (mean arterial pressure <35mmHg for infants between 1000 g and 1499 g and <30mmHg for infants <1000 g) with inotropic support, clinical or proven (culture positive) sepsis, NEC (grade ≥2), and CLD (oxygen dependency beyond 36 weeks of corrected age) with diuretic or steroid were recorded to previously prepared forms. The duration of total parenteral nutrition (TPN), the need of red blood cell transfusion for anemia, oxygen exposure, the number of hyperoxia (PaO_2 ≥100 mmHg), hypoxia (PaO_2 ≤40 mm Hg), and hypercarbia ($PaCO_2$ ≥60 mmHg) episodes prior to onset of ROP were also evaluated.

Ethics

This study was performed with permission from the Keçiören Ethics Committee (Decision number: 144). Eye examinations and LP were performed after taking informed consent from the parents.

Statistical analysis

SPSS 16.0 (SPSS, Chicago, IL) was used for statistical analysis. Kolmogorov-Smirnov test was used to determine the distribution of data. Data are expressed as the arithmetic mean ± standard deviation (SD) or median (min-max), as appropriate. Differences among two groups were analyzed by Student's *t*-test or Mann-Whitney U test. The chi-square test was used to compare the categorical variables. Pearson or Spearman test was used to analyze correlation between variables. The odds ratio (OR) and logistic regression analysis were done with development of ROP as the dependent variable and possible risk factors of interest as independent variables. Multivariate analysis was repeated for need of LP as the dependent variable. The level of significance was set at 5% for all comparisons.

RESULTS

Of the 113 cases included in the study, 60 (53.1%) were male. The median gestational age was 30 weeks (24-36) with a mean birth weight of 1412 ± 473 g. The first ROP examination was performed at 34 ± 3.0 weeks of corrected age.

The patients were divided into two groups according to ROP development. Group 1 (with ROP) included 53 and Group 2 (without ROP) included 60 patients. ROP incidence was 46.9% in the study group. Among patients with ROP, 19 (35.8%) were <1000 g. Sixty patients (53.1%) were in Group 2 (without ROP). Table 1 shows comparison of the patients with and without retinopathy of prematurity.

Comparison of clinical data in the patients according to ROP development

When compared to Group 2, birth weight and gestational age were lower; the rates of associated disorders were significantly higher among patients with ROP. The use of caffeine for apnea and need of inotropic support for hypotension were more frequent in Group 1 (p<0.05). Transfusion rate, number of transfusion, and need of transfusion in the first 10 days of life were higher in the same group (p<0.05). It was noticed that infants with ROP had prolonged oxygen exposure and hyperoxia/hypoxia and hypercarbia episodes before onset of ROP were more frequently detected in Group 1 compared to Group 2 (p<0.05).

There were positive correlations between the age at onset of ROP and gestational age (r=0.47, p=0.001), birth weight (r=0.36, p=0.007).

In multivariate analysis, when possible risk factors for development of ROP were assigned as gestational age, having RDS, PDA and sepsis, use of caffeine, need of transfusion in the first 10 days of life, duration of TPN and total oxygen exposure, it was found that the need of transfusion in the first 10 days of life has increased the risk for ROP (OR: 1.9, 95% CI: 1.1-3.3, p=0.01).

Among patients with ROP, 38 (71.7%) had stage ≤ 2 ROP [stage 1: 30 (26.5%), stage 2: 8 (7.1%)], and 15 (28.3%) had stage ≥ 3 ROP [stage 3: 9 (7.1%), stage 4: 1 (0.9%), stage 5: 2 (1.8%)]. The rate of aggressive ROP was 2.7% (n=3). Plus disease was detected in 14 (26.4%) patients. LP was needed in 18 (33.9%) of patients with ROP.

Table 1. Comparison of the patients with and without retinopathy of prematurity

	Group 1 (with ROP) n=53	Group 2 (without ROP) n=60	p value
Demographic and perinatal data			
Male, n (%)	23 (43.3)	37 (61.6)	0.06
Age, weeks (min-max)	28 (24-35)	31 (26-36)	0.001
Birth weight, gram (mean ± SD)	1223±482	1574±408	0.001
Cesarean rate, n (%)	35 (67.3)	41 (68.3)	0.9
Age at admission, day, (min-max)	1 (1-124)	1 (1-110)	0.34
Associated disorders			
RDS, n (%)	44 (84.6)	36 (60)	0.004
PDA, n (%)	30 (57.7)	19 (31.7)	0.006
IHB, n (%)	46 (88.5)	41 (68.3)	0.01
ICH, n (%)	26 (49.0)	16 (26.7)	0.002
Use of caffeine for apnea, n (%)	36 (69.2)	27 (45)	0.01
Hypotension, n(%)	41 (78.8)	27 (45)	0.001
Clinical sepsis, n (%)	43 (82.7)	45 (75.0)	0.31
Proven sepsis, n (%)	27 (51.9)	21 (35.0)	0.07
NEC, n (%)	27 (51.9)	15 (25.0)	0.003
CLD, n (%)	18 (34.6)	6 (10.0)	0.002
Supportive treatment			
Duration of TPN, day, (min-max)	39 (8-87)	20 (0-113)	0.001
Blood transfusion, n (%)	49 (92.4)	38 (63.3)	0.001
Blood transfusion in the first 10 days of life, n (%)	25 (48.1)	8 (13.3)	0.001
Number of transfusion, (min-max)	4 (0-15)	1 (0-16)	0.04
Oxygen exposure			
Mechanical ventilation, n (%)	44 (84.6)	40 (66.7)	0.01
Duration of mechanical ventilation, day, (min-max)	3 (0-80)	1 (1-102)	0.007
CPAP, n (%)	44 (84.6)	38 (63.3)	0.005
Duration of CPAP, day, (min-max)	6 (0-45)	2 (1-70)	0.001
Free oxygen, n (%)	46 (88.5)	50 (83.3)	0.24
Duration of free oxygen, day, (min-max)	10 (0-143)	5 (1-98)	0.002
Total oxygen exposure, day, (min-max)	42 (3-163)	10 (0-113)	0.001
No of hyperoxia episodes (PaO2 ≥100 mmHg), (min-max)	3 (0-24)	0 (1-10)	0.001
No of hypoxia episodes (PaO2 ≤40 mmHg), (min-max)	0 (0-5)	0 (0-13)	0.04
No of hypercarbia episodes (PaCO2 ≥60 mmHg), (min-max)	0.5 (0-12)	0 (0-13)	0.002
Length of hospital stay, day (min-max)	62 (14-170)	38 (5-164)	0.001

ROP: Retinopathy of prematurity, RDS: Respiratory distress syndrome, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, IHB: indirect hyperbilirubinemia, ICH: intracranial hemorrhage, BPD: bronchopulmonary dysplasia, TPN: total parenteral nutrition

Table 2. Comparison of the clinical data in patients with retinopathy of prematurity according to disease severity and need of laser photocoagulation

	Group 1a (ROP with LP) n=18	Group 1b (ROP without LP) n=35	p value
Demographic and perinatal data			
Male, n (%)	8 (44.4)	51 (53.1)	0.67
Age, weeks (min-max)	28 (24-35)	30 (24-36)	0.007
Birth weight, gram (mean ± SD)	1045 (660-3400)	1490(550-3320)	0.001
Cesarean rate, n (%)	14 (77.8)	62 (57.9)	0.41
Age at admission, day, (min-max)	2.5 (1-124)	1 (1-110)	0.01
Associated disorders			
RDS, n (%)	16 (88.9)	28 (82.4)	0.40
PDA, n (%)	11 (61.1)	19 (55.9)	0.40
IHB, n (%)	11 (61.1)	29 (85.3)	0.30
ICH, n (%)	12 (66.7)	14 (41.2)	0.05
Use of caffeine for apnea, n (%)	14 (77.8)	22 (64.7)	0.20
Hypotension, n (%)	14 (77.8)	22 (64.7)	0.50
Clinical sepsis, n (%)	16 (88.9)	27 (79.4)	0.30
Proven sepsis, n (%)	11 (61.1)	16 (47.1)	0.20
NEC, n (%)	13 (72.2)	14 (41.2)	0.03
CLD, n (%)	9 (50)	9 (26.5)	0.08
Supportive treatment			
Duration of TPN, day, (min-max)	50 (8-74)	24(0-113)	0.006
Blood transfusion, n (%)	10 (55.6)	32 (94.1)	0.20
Blood transfusion in the first 10 days of life, n (%)	6 (33.3)	19 (55.9)	0.60
Number of transfusion, (min-max)	3 (0-11)	4 (0-15)	0.80
Oxygen exposure			
Mechanical ventilation, n (%)	15 (83.3)	29 (85.3)	0.50
Duration of mechanical ventilation, day, (min-max)	8 (0-22)	2 (0-80)	0.10
CPAP, n (%)	15 (83.3)	29 (85.3)	0.30
Duration of CPAP, day, (min-max)	16 (2-45)	4 (0-30)	0.01
Free oxygen, n (%)	15 (83.3)	31 (91.2)	0.03
Duration of free oxygen, day (min-max)	20 (0-80)	9 (0-143)	0.08
Total oxygen exposure, day, (min-max)	51 (4-110)	12 (0-163)	0.001
No of hyperoxia episodes (PaO2 ≥100 mmHg), (min-max)	5 (0-10)	2 (0-24)	0.01
No of hypoxia episodes (PaO2 ≤40 mmHg), (min-max)	0 (0-5)	0 (0-5)	0.08
No of hypercarbia episodes (PaCO2 ≥60 mmHg), (min-max)	3 (0-10)	0 (0-13)	0.001
Length of hospital stay, day, (min-max)	68 (15-128)	45 (5-170)	0.02

ROP: Retinopathy of prematurity, LP: laser photocoagulation, RDS: Respiratory distress syndrome, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, IHB: indirect hyperbilirubinemia, ICH: intracranial hemorrhage, BPD: bronchopulmonary dysplasia, TPN: total parenteral nutrition

Comparison of the clinical data in patients with ROP according to need of laser photocoagulation

Table 2 shows comparison of the clinical data in patients with ROP according to need of LP. The mean birth weight and gestational age were lower in patients with need of LP (p<0.01). Among patients needed LP, 7 (38.8%) were <1000g. Although, the incidence of NEC was higher in Group 1a (p=0.03), the rates of other associated disorders were similar between the two subgroups (p>0.05). The patients in Group 1a had longer durations of TPN and total oxygen exposure (p<0.01). There was no difference according to the number of hypoxia episodes (p>0.05), but hyperoxia and hypercarbia were more frequent in Group 1a (p<0.05).

In logistic regression analysis, it was determined that the higher gestational age and the absence of apnea or prophylactic caffeine use were associated with reduced need of LP [OR: 0.5, 95% CI: 0.2-0.9), p=0.02, and (OR: 0.1, 95% CI: 0.03-0.9), p=0.02), respectively].

Although the median corrected ages at the first ROP examination and onset of ROP were similar between LP subgroups, the median ROP stage at the time of the first examination was greater in Group 1a. The rate of plus disease was also higher in the same group (Table 3).

Table 3. Ophthalmologic findings in patients with retinopathy of prematurity according to need of laser photocoagulation

	Group 1a (ROP with LP) n=18	Group 1b (ROP without LP) n=35	p value
Corrected age at the first ROP examination week, (min-max)	34 (31-36)	33 (28-39)	0.1
Corrected age at onset of ROP, week, (min-max)	35 (33-39)	36 (31-47)	0.5
ROP stage at the time of the first examination, (min-max)	3 (1-5)	1 (1-3)	*0.001*
Plus disease, n (%)	13 (72.2)	1 (2.9)	*0.001*

LP: laser photocoagulation, ROP: Retinopathy of prematurity

DISCUSSION

Despite advances in neonatal care, ROP continues to be an important cause of potentially preventable blindness worldwide. Although the etiopathogenesis of ROP is multifactorial, the most commonly responsible factors are low gestational age and birth weight (4). In this study we investigated the risk factors for the development of ROP in premature infants. The factors affecting the need of LP were also evaluated.

In the CRYO-ROP study, the incidence of ROP was found to be 65.8% in infants who were <1251 g, and 81.6% in infants who were <1000 g (4). Shah et al. (11) found the incidence of ROP as 39.4% in the presurfactant period compared to 25.6% in surfactant period. In a recent research from Turkey, 330 infants with a gestational age of ≤34 weeks were evaluated for ROP. The authors reported that no treatment was needed in infants after 32 weeks of gestation with ROP incidence of 32.1% (12). In the current study, the infants with a gestational age of <32 weeks and 32-37 weeks but at high risk for ROP were examined. We found ROP incidence as 46.9%. Among patients with ROP 19 (35.8%) were <1000 g. LP was needed in 18 (33.9%) of patients with ROP.

Traditionally, it is recommended for all infants with a gestational age of <32 weeks and a birth weight of <1500 g to be screened for ROP. However, ROP development due to environmental factors has been reported in infants who were >32 weeks (13). In our study, ROP was identified in 25% of infants with a gestational age between 32-37 weeks. This demonstrates that, independently from the gestational age, other risk factors also play a significant role in the development of ROP.

As observed in our study, RDS and CLD are known to be increased the risk of ROP due to hypoxia and the need for oxygen therapy. There are different opinions regarding the effects of surfactants on the development of ROP. Although it has been reported to provide pulmonary stability by reducing the duration of mechanical ventilation, and thus to reduce the prevalence by decreasing risk factors associated with ROP, there are also publications claiming that it increases the frequency of ROP (14,15). In our study, ROP incidence was observed to be higher in infants who were treated by prophylactic or therapeutic surfactant. This may be due to the fact that surfactant therapy increases the survival rate. In these cases, it was assumed that the higher incidence of the ROP was caused by exposure to hyperoxia resulting from the sudden increase in arterial oxygen pressure along with surfactant administration at early stage in life.

One of the main factors in the pathogenesis of ROP is hyperoxia. During intrauterine life, the fetus' arterial oxygen pressure is between 30-35 mmHg. This value increases to 60-80 mmHg soon after birth. In addition, hyperoxia, which is caused by respiratory support given to premature infants for respiratory problems, suppresses the release of the vascular endothelial growth factor (VEGF) in the premature retinal blood vessels and prevents retinal vascularization (16). In our study, we observed that the infants with ROP had prolonged oxygen exposure. Total oxygen exposure was also higher among infants who needed LP. Although hypercarbia has also been reported in experimental studies as a risk factor for the ROP development, the results of certain clinical trials are controversial (17). We showed that episodes of hypercarbia were observed more frequently in cases that developed ROP, suggesting that carbon dioxide may cause retinopathy with mechanisms similar to those of oxygen.

Another condition that leads to ROP is apnea. Apnea is a paradoxical response to hypoxia resulting from the insufficient stimulation of the respiratory center due to immaturity. Nowadays, one of the most commonly drugs used for the treatment of apnea of prematurity is caffeine. Caffeine was reported to decrease the incidence of CLD and to improve the neurodevelopmental outcomes (18). Although the relation between ROP and apnea is well known, there is limited number of studies investigating the effects of caffeine on the development of ROP. In these studies, caffeine was demonstrated to have no effect on the incidence of ROP (19). However, in our study, the incidence of ROP was higher among infants having prophylactic or therapeutic caffeine. While the reason for this observation is not very clear, it is probably due to frequent apneic episodes.

It is reported that the presence of significant PDA can lead to ROP. The shunt which develops from the aorta towards the pulmonary artery in symptomatic PDA causes hypoxia in peripheral tissues. Although some studies claim that PDA is not associated with ROP, the majority of research suggest that it increases the incidence of ROP (5,6,20). In our study, the incidence of PDA was found to be higher among those with ROP.

In our study, we demonstrated that red blood cell transfusion in the first 10 days of life adversely affected the ROP development. As the blood used in transfusions contains adult-type hemoglobin, a higher percentage of oxygen is consequently sent to the tissues.

It is known that this situation facilitates the development of the ROP by damaging effect on the retinal blood vessels (21). Erythrocytes in donor blood are short-lived, and their withdrawal from circulation leads to the storage of their iron; this in turn plays a role in the development of ROP. Protection from free iron is ensured by transferrin, but the level of this protein is very low in the premature infants. In the study of Inder et al. (22), it was determined that excessive erythrocyte transfusion to very low birth weight premature infants leads to an increase in serum iron and transferrin saturation, causing an increase in ROP risk independently from gestational age, postnatal steroid use and the number of oxygen treatment days. In the same study, serum iron has been shown to play a role as a strongly oxidative agent that triggers lipid peroxidation by converting radicals of low reactivity, such as hydrogen peroxide and superoxide, into highly reactive hydroxyl radicals.

There are rare studies investigating the risk factors for need of laser in patients with ROP. Alpay et al. (12) reported RDS and low gestational age to be the most important risk factors in patients requiring LP. Thomas et al. (23) have observed a higher need of LP treatment among ROP patients with more frequent pre-LP desaturation and with a high degree of oxygen saturation variability. Ikeda et al. (24) have found that ROP patients in need of LP treatment had a higher incidence of sepsis, blood transfusions and surfactant administration. In our study, patients with ROP were also divided into two subgroups according to need of LP, and both subgroups were compared for clinical data. The mean birth weight and gestational age were lower in patients with need of LP. The patients in LP group had longer durations of TPN and total oxygen exposure Hyperoxia and hypercarbia were more frequent in these patients. Thomas et al. (25), have identified late neonatal sepsis as an independent risk factor in patients with pre-threshold/threshold ROP and plus disease.

In our study, although there was no difference according the sepsis rate, the frequency of NEC was found to be higher in the group requiring LP. NEC is a condition associated with bowel infarction in which proinflammatory cytokines play an important role. The higher need for LP in cases with NEC may be due to the association of the bowel infarction with general hypoxia. It has been suggested that, in the presence of systemic infection, damage and proinflammatory cytokine release in the newly developing retinal blood vessels may lead to VEGF release and contribute to severe ROP development.

CONCLUSION

Since ROP is known to be multifactorial, each field should determine and establish its own risk factors. Although low birth weight and early gestational age are important risk factors, red blood cell transfusion in early neonatal period may contribute to the development of ROP.

Conflict of Interest
No conflict of interest was declared by the authors.

REFERENCES

1. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vasculer sheat behind each crystalline lens. Am J Ophthalmol 1942; 25: 203-4.
2. Araz-Ersan B, Kir N, Akarcay K, et al. Epidemiological analysis of retinopathy of prematurity in a referral centre in Turkey. Br J Ophthalmol 2013; 97: 15-7.
3. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006; 117: 572-6.
4. Palmer EA, Schaffer DB, Plotsky DF. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Prognostic factors in the natural course of retinopathy of prematurity. Ophthalmology 1993; 100: 230–7.
5. Altunbaş HH, Kır N, Ovalı T, Dağoğlu T. Prematüre Retinopatisi Klinik Seyir ve Risk Faktörleri. Turk J Ophthalmol 2002; 32: 286-98.
6. Ilıkkan DY, Vural M, Karaçorlu M, Ilıkkan B, Perk Y, İlker Ö. Prematüre bebeklerde retinopati taraması. Cerrahpaşa Tıp Fakültesi Verileri. Çocuk Sağlığı ve Hastalıkları Dergisi 2000; 44: 122-7
7. Ciechan J, Gerkowicz M, Wróblewska E. The prognostic significance of shape of demarcation line and ridge in clinical course of active phase of retinopathy of prematurity. Klin Oczna 2003; 105: 392-4.
8. Talu S, Cormos D, Zaharia G, Stefanut C, Popa M, Lucaci DI. Prognostic factors for laser treatment in retinopathy of prematurity. Oftalmologia 2011; 55: 84-9.

9. International Committee for the Classification of Retinopathy of Prematurity. The International classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005; 123: 991–9.

10. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003; 121: 1684–94.

11. Shah VA, Yeo CL, Ling YL, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. Ann Acad Med Singapore 2005; 34: 169-78.

12. Alpay A, Uğurbaş SH. Incidence and risk factors for retinopathy of prematurity in the West Black Sea region, Turkey. Turk J Pediatr 2012; 54: 113-8.

13. Fielder AR., Shaw DE., Robinson J, Ng YK. Natural history of retinopathy of prematurity: a prospective study. Eye 1992; 6: 233-242

14. Termote JU, Schalij-Delfos NE, Wittebol-Post D, Brouwers HA, Hoogervorst BR, Cats BP. Surfactant replacement therapy: a new risk factor in developing retinopathy of prematurity? Eur J Pediatr 1994; 153: 113-6.

15. Ved GP, Upreet D, Rohit S, Piyush G, Jolly R. Retinopathy of prematurity-Risk factors. Indian J Pediatr 2004; 71: 887-92.

16. Tlucek PS, Grace SF, Anderson MP, Siatkowski RM. Effect of the oxygen saturation target on clinical characteristics of early- versus late-onset retinopathy of prematurity. Journal of AAPOS 2012; 16: 70-4.

17. Gellen B, McIntosh N, McColm JR, Fleck BW. Is the partial pressure of carbon dioxide in the blood related to the development of retinopathy of prematurity? Br J Ophthalmol 2001; 85: 1044-5.

18. Greenough A, Ahmed N. Perinatal prevention of bronchopulmonary dysplasia. J Perinat Med 2013; 41: 119–26

19. Mueni E, Opiyo N, English M. Caffeine for the management of apnea in preterm infants. Int Health 2009; 1: 190–5.

20. Allegaert K, Coen K, Devlieger H. On behalf of the Epibel Study Group Threshold retinopathy at threshold of viability. The Epibel Extended Report. Br J Ophtalmol 2004; 88: 239-42.

21. Dani C, Reali MF, Bertini G, Martelli E, Pezzati M, Rubaltelli FF. The role of blood transfusions and iron intake on retinopathy of prematurity. Early Hum Dev 2001; 62: 57-63.

22. Inder TE, Clemett RS, Austin NC, Graham P, Darlow BA. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. J Pediatr 1997; 131: 541-4.

23. Thomas WJ, Rauser M, Dovich JA, Dustin L, Flaxel CJ. Oxygen saturation in premature infants at risk for threshold retinopathy of prematurity. Eur J Ophthalmol 2011; 21: 189-93.

24. Ikeda H, Kuriyama S. Risk factors for retinopathy of prematurity requiring photocoagulation. Jpn J Ophthalmol 2004; 48: 68-71

25. Thomas WJ, Rauser M, Dovich JA, Dustin L, Flaxel CJ. Oxygen saturation in premature infants at risk for threshold retinopathy of prematurity. Eur J Ophthalmol 2011; 21: 189-93.