·Clinical Research·

# One -year experience in the retinopathy of prematurity: frequency and risk factors, short-term results and follow-up

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## Abstract

• AIM: As a result of the increase in premature births and the advances in neonatal intensive care, retinopathy of prematurity (ROP) remains one of the most important causes of childhood blindness worldwide. The main factors in the development of ROP are gestational age, birth weight and oxygen therapy. ROP continues to gain importance due to the increasing survival rates of more immature babies.

• METHODS: Between January 2007 and October 2008, 203 premature infants treated at the Neonatal Intensive Care Unit (NNICU) were prospectively enrolled and the relationship between known risk factors and the occurance of ROP was studied.

• RESULTS: ROP in various stages developed in 86 cases (42.4% ). Statistically significant correlations were found between the development of ROP and birth weight ($P$< 0.0001) gestational age ($P$<0.0001), oxygen treatment and its duration ($P$<0.0001 and $P$=0.002), mechanical ventilation (MV) and its duration ($P$=0,0001 and $P$=0.0001), apnea($P$= 0.001), intraventricular hemorrhage (IVH) ($P$=0.046), sepsis ($P$=0.0001), use of erythropoietin (EPO) ($P$=0.003), the number of blood transfusions and frequency ($P$=0.0001 and $P$=0.0001), surfactant application ($P$=0.0001), the presence of patent ductus arteriosus (PDA) ($P$=0.001) or bronchopulmonary dysplasia (BPD) ($P$ =0.0001). No significant correlations were found between the occurance of ROP and maternal pre-eclampsia ($P$=0.293), multiple pregnancy ($P$= 0.218), or hyperbilirubinemia ($P$=0.494). Severity of ROP was related significantly with birth weight ($P$=0.0001), but no significant correlation between severity of ROP and gestational age was present.

• CONCLUSION: Early description and reduction of the risk factors related with the occurance of ROP with the help of routine screening programs may warrant the prevention of visual loss, however early ophthalmic diagnosis and treatment are still mandatory to provide better visual rehabilitation.

• KEYWORDS: prematurity; retinopathy;risk factors; gestational age; birth weight; oxygen therapy

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## INTRODUCTION

The retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy that develops in the immature infants as a result of retinal vessel pathology. It is among the most important causes of childhood blindness in developed countries [1,2]. Even though different etiological factors may affect the occurance of ROP, the principal one is local retinal ischemia and triggered neovascularization. In late phase, retinal detachment can be seen as a result of traction of cicatricial tissue. In more than 90% of cases in the acute phase of the disease regress spontanously, leaving minimal scar tissue without causing a significant visual loss, however in less than 10% of cases, retinal detachment and related blindness may occur[3].

Although the well-known main factors in the occurance of ROP are gestational age, birth weight and oxygen therapy,

seldom development of ROP is also described in the lack of oxygen therapy [2]. It has been reported that many other factors, such as blood transfusions, intraventricular hemorrhage (IVH), apnea, sepsis, hypercarbia or hypocarbia, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD) and perinatal asphyxia may affect the occurence of ROP [2-4]. The objective of the present study was to determine the frequency, clinical course and risk factors of ROP in premature infants treated in the Neonatal Intensive Care Unit (NNICU) of our hospital. Evaluation of both the treatment results in patients with stage 3 or over ROP, and the development of ocular disorders in study patients at one year of age, were also performed.

## MATERIALS AND METHODS

**Materials** Two-hundred and three premature infants treated between January 2007 and October 2008 in the NNICU of Dr Behçet Uz Childrens' Hospital, a tertiary referral clinic in Izmir-Turkey, were enrolled in this prospective study. History of maternal pre-eclampsia and multipl delivery, sex, birth weight, gestational age, oxygen therapy and its duration, mechanical ventilation (MV) and its duration, number of blood transfusions, history of erythropoietin (EPO) treatment and the presence of IVH, sepsis, PDA, hyperbilirubinemia necessitating phototherapy, BPD, as well as apnea requiring treatment were recorded for each infants.

**Methods** Initial ophthalmic evaluations and the regular follow-up examinations were performed by the same ophthalmologist according to the 2006 AAP guidelines for screening ROP [5]. Initial fundoscopic examination was performed at 4 weeks after birth for each cases. Pupillary dilation was accomplished with one drop of 2.5% phenylephrine and 0.5% tropicamide, repeated in approximately ten minutes, with fundoscopy performed after 45 minutes. Topical anesthesia was provided with proparacaine HCl 0.5% drops. ROP stages ranging from I to V, were evaluated with binocular indirect ophthalmoscopy and recorded. Until the vascularization of zone 3, premature infants with the lack of retinopathy were followed at 2-4 weeks of intervals, and babies with stage 1 or 2 ROP were evaluated every 1-2 weeks, however cases with stage 3 ROP were examined twice weekly [5]. All cases with stage 3 or more advanced disease were referred for treatment to the specialized retina centers. Infants with the diagnosis of threshold disease underwent diode laser photocoagulation (LP) under general anesthesia within 72 hours. Patients treated with LP were followed up twice weekly; in case of a tendency to progression of threshold disease, treatment with LP was repeated. Patients with regressive retinopathy after LP were evaluated at 1-2 weeks of intervals according to the status of plus disease. Cases with disease progression into stage 4B or 5 were subjected to vitreoretinal surgery. The results of referred patients were obtained from the centers where they had been followed. All cases were re-evaluated at one year of age by the same ophthalmologist, whether they had developed ROP or not.

Cases were considered in four groups according to the birth weight: 1000 grams or less, 1001-1250 grams, 1250-1500 grams and more than 1500 grams. The three groups according to the gestational age were as follows: up to 28 weeks, 29-32 weeks, 33 weeks or more. The duration of oxygen therapy and MV were also recorded and evaluated in order to study their effect on the occurance of ROP.

**Statistical Analysis** All the collected data were evaluated with the SPSS 15.0 for Microsoft Windows statistical package. Descriptive statistics for the different characteristics such as the birth weight or gestational age of patients were prepared with the software. Relationships involving two discrete variables were evaluated using the chi-squared or Fisher's exact test. Student's $t$-test was used to evaluate the relationships between two groups of a continuous variable and a one-sided ANOVA was used for testing multiple groups. The p-value limit for statistical significance of a correlation was set at 0.05. A logistic regression analysis was performed to evaluate the variables influencing the presence of ROP, and an odds ratio was calculated, with its 95% confidence interval. Risk factors were accepted as significant if their confidence limits did not include the value 1. The present study was conducted in complience with the principles of the 2008 Decleration of Helsinki.

## RESULTS

Of the 203 infants included in the study, 92 (45.4%) were female and 111 (54.6%) were male. The mean birth weight was 1582.56 ±44.39 grams (620-2800), and the mean gestational age was 31.11 ±2.63 weeks (26-37). ROP in various stages developed in 86 cases (42.4% ). The distribution of disease stages are shown in Table 1 and 2.

Lower birth weight was significantly correlated with increased ROP frequency ($P$<0.0001). Distribution of ROP stages according to the birth weight is shown in Table 3. A significant correlation between birth weight and the severity of ROP was also found ($P$=0.0001) which is shown in Table 4. Development of ROP was significantly more frequent in lower gestational age ($P$<0.0001), furthermore ROP and severe ROP was seen much more common in babies born before the 28th week of gestation (Table 5, 6). An univariate analysis of correlation with the development of ROP was performed for each presumed risk factor, and the results are presented in Table 7.

**Table 1 Presence of ROP and the distribution of ROP stages in study infants**

| PR | Infant (n) | % |
|---|---|---|
| No ROP | 117 | 57.7 |
| Stage I | 48 | 23.63 |
| Stage II | 32 | 15.74 |
| Stage III | 5 | 2.45 |
| Stage IV-V | 1 | 0.48 |
| Total | 203 | 100 |

**Table 2 The distribution of stages in study infants with ROP**

| Stage | Infant (n) | % |
|---|---|---|
| Stage I | 48 | 55.82 |
| Stage II | 32 | 37.21 |
| Stage III | 5 | 5.81 |
| Stage IV-V | 1 | 1.16 |
| Total | 86 | 100 |

**Table 3 The correlation between birth weight and the severity of ROP in study infants**

| Birth Weight | Infant (*n*) | ROP (*n*) | % |
|---|---|---|---|
| ⩽1000 gr | 18 | 14 | 77.77 |
| 1001-1250 gr | 34 | 23 | 67.64 |
| 1251-1500 gr | 40 | 22 | 55 |
| >1500 gr | 111 | 27 | 24.32 |
| Total | 203 | 86 | 42.36 |

*P*<0.0001

**Table 4 The distribution of stages accorrding to birth weight in study infants**

| Birth Weight | Stage I *n* (%) | Stage II *n* (%) | Stage III *n* (%) | Stage IV-V *n* (%) |
|---|---|---|---|---|
| ⩽1000 gr | 8 (44.4) | 5 (27.8) | 0 (0) | 1 (5.6) |
| 1001-1250 gr | 17 (50) | 5 (14.7) | 1 (2.9) | 0 (0) |
| 1251-1500 gr | 12 (30) | 8 (20.0) | 2 (5.0) | 0 (0) |
| >1500 gr | 11 (9.9) | 14 (12.6) | 2 (1.8) | 0 (0) |

*P*=0.0001

**Table 5 The frequency of ROP according to gestational age in study infants**

| Gestational Age | Infant (*n*) | Infant with ROP (*n*) | % |
|---|---|---|---|
| ⩽28 weeks | 46 | 36 | 78.26 |
| 29-32 weeks | 93 | 37 | 39.78 |
| ⩾33 weeks | 64 | 13 | 20.31 |
| Total | 203 | 86 | 42.36 |

*P*<0.0001

**Table 6 The distribution of stages according to gestational age**

| Gestational Age | Stage I *n* (%) | Stage II *n* (%) | Stage III *n* (%) | Stage IV-V *n* (%) | Total *n* (%) |
|---|---|---|---|---|---|
| ⩽28 weeks | 24 (66.7) | 10 (27.76) | 1 (2.77) | 1 (2.77) | 36 (100) |
| 29-32 weeks | 15 (40.54) | 18 (48.64) | 4 (10.82) | 0 (0) | 37 (100) |
| ⩾33 weeks | 9 (69.23) | 4 (30.77) | 0 (0) | 0 (0) | 13 (100) |
| Total | 48 (55.82) | 32 (37.20) | 5 (5.82) | 1 (1.16) | 86 (100) |

*P*<0.0001

However oxygen therapy was found to be a risk factor for ROP development ($P$=0.0001), maternal pre-eclampsia, multipl delivery and hyperbilirubinemia did not significantly affect the ROP frequency ($P$=0.293, $P$=0.218, $P$=0.494, respectively). The mean duration of oxygen therapy was

**Table 7 The correlation between ROP and risk factors**

| Variable | ROP(+) *n* (%) | ROP(-) *n* (%) | *P* |
|---|---|---|---|
| Maternal preeclampsia (+) | 11 (50) | 11 (50) | |
| Maternal preeclampsia(-) | 75 (41.4) | 106 (58.6) | 0.293 |
| Multiple pregnancy (+) | 22 (37.3) | 37 (62.7) | |
| Multiple pregnancy (-) | 64 (44.4) | 80 (55.6) | 0.218 |
| Oxygen (+) | 65 (53.3) | 57 (46.7) | |
| Oxygen (-) | 21 (25.9) | 60 (74.1) | 0.0001 |
| Mechanical Ventilation (+) | 43 (71.7) | 17 (28.3) | |
| Mechanical Ventilation (-) | 43 (30.1) | 100 (69.9) | 0.0001 |
| Sepsis (+) | 33 (71.7) | 13 (28.3) | |
| Sepsis (-) | 64 (40.8) | 104 (66.2) | 0.0001 |
| Blood Transfusion (+) | 64 (63.4) | 37 (36.6) | |
| Blood Transfusion (-) | 22 (21.6) | 80 (78.4) | 0.0001 |
| IVH (+) | 30 (52.6) | 27 (47.4) | |
| IVH (-) | 56 (38.4) | 90 (61.6) | 0.046 |
| Surfactant (+) | 34 (70.8) | 14 (29.2) | |
| Surfactant (-) | 52 (33.5) | 103 (66.5) | 0.0001 |
| Hyperbilirubinemia (+) | 48 (42.9) | 64 (57.1) | |
| Hyperbilirubinemia(-) | 38 (41.8) | 53 (58.2) | 0.494 |
| PDA (+) | 51 (55.4) | 41 (44.6) | |
| PDA (-) | 35 (31.5) | 76 (68.5) | 0.001 |
| Apnea (+) | 43 (56.6) | 33 (43.4) | |
| Apnea (-) | 43 (33.9) | 84 (66.1) | 0.001 |
| EPO (+) | 27 (61.4) | 17 (38.6) | |
| EPO (-) | 59 (37.1) | 100 (62.9) | 0.003 |
| BPD (+) | 13 (100) | 0 (0) | |
| BPD (-) | 73 (38.4) | 117 (61.6) | 0.0001 |

7.05±13.6 days in patients with any stage of ROP, whereas it was found as 2.35 ±3.13 days in cases with normal fundoscopy. The correlation between the duration of oxygen therapy and the frequency of ROP was statistically significant ($P$=0.002). A mild correlation was also found between the duration of oxygen therapy and the severity of ROP ($P$<0.05). On the other hand, both the use of MV and its duration were significantly correlated with ROP development ($P$=0.0001, $P$=0.0001). The mean duration of MV was 2.28±7.16 days in patients with any stage of ROP, whereas it was found as 0.49±1.49 days in the rest of the study group. A correlation was also evident between the duration of MV and the severity of ROP ($P$<0.05).

During their hospitalization, 101 cases received blood transfusion. ROP incidence was found to be significantly increased with blood transfusion and its frequency ($P$= 0.0001, $P$=0.0001). The mean number of blood transfusions was 1.22±2.12 in patients with any stage of ROP, whereas it was found as 0.46±0.80 in the rest of the study population. A mild correlation was found between the number of blood transfusion and the severity of ROP ($P$<0.05). Furthermore prolonged oxygen therapy and MV duration, as well as increased neccessity to blood transfusion were found in cases with ROP stage 4 (44 days, 36 days, and 10

**Table 8 Multivariate analysis of risk factors for the development of acute ROP**

| Variable | *P* | Odds ratio | 95 % CI |
|---|---|---|---|
| BW 1000-1250 grams | 0.0001 | 4.257 | 1.577-11.489 |
| Duration of oxygen therapy | 0.0001 | 1.203 | 1.102-1.313 |
| The number of blood transfusions | 0.0001 | 1.729 | 1.181-2.529 |

transfusions, respectively). ROP frequency was also significantly related with sepsis ($P$=0.0001), BPD ($P$ = 0.0001), apnea ($P$=0.001), EPO treatment ($P$=0.003), surfactant treatment ($P$=0,0001), IVH ($P$=0,040) or PDA ($P$= 0.001) (Table 7).

In order to determine the conditions that increase ROP incidence, a logistic regression analysis was performed. Besides the duration of oxygen therapy and birth weight were strongly correlated with ROP incidence, the number of blood transfusions was found to be the most important risk factor for the occurance of ROP. Retinopathy incidence was multiplied by 1.729 for each blood transfusion and 1.203 for each day of oxygen administration. The risk of ROP occurance for infants weighting 1000-1250 grams was 4.257 times higher than the rest (Table 8).

Of 86 cases with ROP, 74(86.0%) did not necessitate treatment while threshold disease was diagnosed in 12 (14.0%) cases who underwent diode laser treatment under general anesthesia. Disease regression was seen in 11 (91.7%) of the patients treated with LP, but stage 5 ROP was developed in one case (8.3%). Unfortunately, treatment of this patient with stage 5 ROP with vitreoretinal surgery was unable to prevent blindness. Strabismus, myopia, hyperopia, or amblyopia were present in 10 (11.6%) of the cases with any stages of ROP at the first year of follow-up, whereas such ocular disorders were evident in only 3 (2.6%) of the cases without retinopathy. With respect to the development of ROP, no statistically significant difference was found in the frequency of ocular findings at the first year of follow-up.

## DISCUSSION

The incidence of ROP has increased in the last decades because of the increased frequency of premature births relevant to the developments in assisted reproduction techniques, and the advances in neonatology that allows a great improvement in survival rates of more immature neonates [6,7]. Although various risk factors may trigger the occurance of retinopathy in a premature newborn, the most important causes are lower gestational age and weight [8,9]. The overall frequency of ROP which was inversely correlated with birth weight and gestational age, was 42.4% in our study that was relevant with the literature. The incidence of ROP in Turkish population was reported as 59.0% in cases with a gestational age lower than 28 weeks, 24.3% in cases who were born between 29 and 32 weeks, as well as 6.8% in cases born between 33 and 36 weeks of gestation [10]. ROP frequency was published in the CRYO-ROP study as 83.4% in babies born before the 27th week of gestation, 55.3% in cases with a gestational age between 28 and 31 weeks, as well as 29.5% in babies born after the 31st week of gestation [9]. These rates were reported as 89.0%, 51.7%, and 14.2%, respectively by the Early Treatment for Retinopathy of Prematurity (ETROP) Study Group [11]. In our study, ROP incidence was 78.3% in infants with a gestational age under 28 weeks, 40% in cases who were born between 29 and 33 weeks, and 19.4% in babies born after the 33rd week of gestation which were relevant with the literature.

In a study of 2699 premature newborns, stage 1, 2, and 3 ROP were reported as 25.2%, 21.2%, and 18.3%, respectively by Palmer *et al*[12]. These rates were found as 29.9%, 16.3%, and 6.4% respectively by Fielder *et al*, however stage 4 and 5 ROP were found as 0.3% [13]. Todd *et al* [14] published the frequency of stage 1 and 2 ROP as 39.8%, stage 3 ROP as 14.1%, and stage 4 ROP as 5.3%. Stage 1, 2, 3, and 4 ROP incidence were reported as 50.0%, 36.6%, 10.0%, and 3.3%, respectively in a population based study conducted in our country [7]. Stage 1, 2, and 3 ROP frequency were found as 55.8%, 37.2%, 5.8% in our study, however 1.2% of the study patients had stage 4 or 5 ROP.

The risk of ROP occurance may be increased by triggered intrauterine stress related with pre-eclampsia [15]. However in our study, ROP incidence was almost the same whether the mothers had experienced with pre-eclampsia or not. No statistically significant correlation between ROP occurance and maternal pre-eclampsia was found in the present study. Multiple pregnancy was also thought as a risk factor for the development of ROP, but no statistically significant correlation between ROP occurance and multiple pregnancy was found in our study which is in accordance with the previous studies of Friling *et al*[16] and Brown *et al*[17].

However oxygen therapy is a well-known risk factor for the development of retinopathy in premature infants, there are no evidence-based medicine data to indicate which duration or concentration of oxygen, or which kind of patients would definitely make it a causative factor. The fact also be considered that oxygen therapy is not a necessary factor for

the development of ROP. Furthermore, ROP was reported in 95 infants without ever receiving oxygen therapy by Lucey and Dangman [18]. In our study, the incidence of ROP among infants who received oxygen therapy during a period that varied from 1 to 110 days was 53.3%, whereas it was found as 25.9% in cases without ever receiving oxygen therapy. Similarly, the incidence of ROP among infants who underwent MV was 71.7%, whereas it was found as 30.1% in those who did not receive MV. A significant correlation also persisted between any oxygen therapy administered by MV and the frequency of ROP. The pulsatile character of carbon dioxide levels that manifests itself as intermittant episodes of hypocarbia and hypercarbia should also be considered as an another effect of MV which can not be totally avoided even with the close follow-up of blood gas analysis of the patients. Evaluation of both oxygen therapy and MV duration together showed that an increase in the duration of oxygen therapy was parallel to an increase in the risk of ROP occurance.

The administration of blood transfusion containing adult hemoglobine which allows easier dissociation of loosely bound oxygen than fetal hemoglobin, increases the oxidative damage to retinal capillaries. Studies provided the evidence of a significant correlation between blood transfusion and the development of ROP[19-23].

On the other hand, no significant correlation was found between blood transfusion and the occurance of ROP by Valieva *et al* [24]. In our study, ROP incidence was 63.4% in transfused patients, whereas it was found as 21.6% in nontransfused cases, and blood transfusion was found as one of the most significant risk factors for the development of ROP, so the policies limiting blood transfusion in the preterm newborn gain even greater importance when considering this result.

Mittal *et al*[25] hypothesized that systemic infections could be related with the development of ROP. Besides, increased release of pro-inflammatory cytokines due to systemic infections causes damage in retinal vessels, increased production of angiogenic substances, such as vascular endothelial growth factor (VEGF) may trigger neovascularization. Brown *et al*[17] and Holmstrom *et al*[26] reported a significant increase in ROP incidence in cases with sepsis. ROP frequencies were found as 58.3% and 23.0% in cases with or without sepsis respectively in a study conducted by Gezer *et al*[10] who reported a significant correlation between sepsis and the development of ROP. In the present study, ROP incidence was 71.7% in cases who experienced with sepsis, whereas 40.8% of the rest developed retinopathy, so a statistically significant correlation between sepsis and the occurance of ROP was found. By the way, it always ought to be recommended that sepsis was much more common in cases with lower birth weight and septic patients had greater need for oxygen therapy.

Some authors suggest that presence of IVH tended to increase the ROP frequency by creating tissue hypoxia in the primary avascular retina. Tissue damage via hypoxia and free oxygen radicals, as well as vascular immaturity may trigger the development of retinopathy in premature infants with IVH [1,27]. While ROP was detected in 52.6% of cases with IVH, 38.4% of the cases who did not have ventricular hemorrhage devoloped retinopathy, so a statistically significant correlation was also found between the presence of IVH and the occurance of ROP, in our study.

Oxidative injury is a well-known pathogenetic mechanism for the development of ROP [1,2,3,28]. Considering that bilirubin is the most potent antioxidant known in vitro, it could be speculated that the newborn with high bilirubin levels might be in a reduced risk group for ROP occurance, however no significant correlation have been reported between plasma bilirubin leves and ROP incidence [29,30]. In the present study, ROP incidence was 42.9% in cases with hyperbilirubinemia, whereas 41.8% of the rest developed retinopathy, and no significant correlation between hyperbilirubinemia and the occurance of ROP was evident. On the other hand, Altunbas *et al* reported a statistically significant increase in ROP frequency among the cases with hyperbilirubinemia [31]. As their study cases were more frequently in need of oxygen therapy and more likely to have an indication to blood transfusion or exchange transfusion, the authors suggested to use multivariate regression analysis in stead of univariate analysis which failed to control the mutual interaction among the various risk factors.

The effect of surfactant use on ROP occurance is unclear. It has been reported that surfactant might reduce the incidence of ROP by shortening the weaning period of the infant from MV due to improved pulmonary stability [32]. On the other hand, better survival rates of surfactant treatment may increase the risk of ROP occurance. Even though, some authors suggested a reduced risk for ROP development in cases treated with surfactant, many others could not state any correlation between such treatment and ROP incidence [33-35]. ROP was diagnosed in 70.8% of the babies who received surfactant treatment, while only 33.5% of the rest developed retinopathy; furthermore a statistically significant correlation between surfactant treatment and the risk of ROP occurance was found in our study.

Periods of apnea as well as relevant hypoxia in a premature infant may also trigger the development of ROP, and

increased ROP frequency was documented in cases who experienced with the episodes of apnea [35]. A higher rate of ROP incidence was found in the present study among the babies with apnea, and the correlation was also statistically significant. This could be a consequence of the increased oxygen exposure related with the episodes of apnea.

Because of the reduction of the need for blood transfusion, as well as prevention Fenton's reaction mediated by iron, the use of EPO in premature newborn may play an antioxidant role and inhibate the development of ROP [36,37], however some authors indicated the increased ROP incidence in cases who had to use recombinant EPO [38]. We observed a negative influence of EPO treatment on ROP frequency in the present study in which a birth weight less than 1250 grams and/or gestational age below 32 weeks were common among the patients who undergone EPO treatment.

In our study, disease regression was found as 91.3% in cases with any stage of ROP. The spontaneous regression of ROP reported 50% -90% in several studies [39,40]. Ablation of avascular areas by LP removes hypoxic retina so inhibates the secretion of vasoproliferative substances such as VEGF that impaire vasoproliferation in both vascular and avascular retina. It also leads to a significant regression of acute neovascularization [41]. The success rate of diode laser treatment in the present study was also encouraging which was relevant with the literature.

Many authors reported the increased frequency of myopia in premature infants which was about 29%-50% in the cases with ROP, and 10%-15% in the cases without retinopathy. A correlation was also reported between myopia and ROP severity [42]. An increased frequency of myopia was found in patients with stage 3 or higher ROP by Pennefather *et al*[43]. Myopia was dignosed in 36.4% of the cases with ROP by Kutluk *et al*, however it was found in only 8.5% of their premature patients without retinopathy [44]. Although hyperopia should be diagnosed in 5.4%-22.4% of the cases with ROP and 3.0%-19.1% of the premature cases without retinopathy, no significant correlation between hyperopia and ROP occurance has been found in the literature [44-47]. Both hyperopia and myopia were not statistically correlated with the incidence of ROP in our study.

Up to date, many authors have documented the increased frequency of strabismus in premature children. Because of the delay in the development of macular reflex in premature infants, regressed ROP may also lead to strabismus. The deficiency in the development of central nervous system secondary to prematurity may also be related with increased strabismus frequency due to the disturbances of binocular vision. Another proposed etiology for the deficiency in binocular vision is the presence of ocular disorder that can affect visual acuity such as refractive errors and optic atrophy [42,44-46]. Strabismus incidence was reported as 11.5%-31% in patients with ROP, and 6%-25% in premature infants without retinopathy, while it was published as 2.5% in the controls [42,45]. However ROP was not found as a risk factor for strabismus in a study conducted in Turkey by Kutluk *et al* which might be related with small study population [44]. A strabismus incidence of 5.8% was found in our cases with ROP.

Because of the increase in the frequency of ROP occurance due to the improvement in survival rates of premature infants with very low birth weight, risk factors for the development of retinopathy should be well-known in order to prevent irreversible visual loss. Preventable or modifiable risk factors, also identified by the present study, such as blood transfusion or oxygen therapy ought to be well-managed and routine screening programs for premature newborns must become widespread. Early diagnosis and treatment for retinopathy are also mandatory to prevent blindness and provide better visual rehabilitation in premature infants.

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