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ORIGINAL ARTICLE

Effective Risk Factors in the Development of Retinopathy of Prematurity, Screening Results and Intravitreal Ranibizumab Treatment

Baran Cengiz Arcagök[1], Berna Özkan[2]

[1]Division of Neonatology, Department of Pediatrics, Acibadem Mehmet Ali Aydinlar University Faculty of Medicine, Istanbul, Turkey
[2]Department of Ophthalmology, Acibadem Mehmet Ali Aydinlar University Faculty of Medicine, Istanbul, Turkey

Abstract

Introduction: The aim is to evaluate the incidence of retinopathy of prematurity within three years in premature babies followed up in our clinic, to determine the risk factors that play a role in the development of retinopathy, to evaluate intravitreal ranibizumab treatment and its results.

Methods: Babies with a birth weight of ≤32 weeks and/or a birth weight of ≤1500 grams and babies determined to be at risk by the clinician were examined for the development of retinopathy. Risk factors including week of birth, birth weight, mode of delivery, gender, APGAR scores, need for mechanical ventilation, ≥40% oxygen therapy, duration of oxygen therapy, surfactant therapy, acidosis, hypoxia, sepsis, erythrocyte transfusion, intraventricular hemorrhage, apnea and anemia were compared between cases who developed or did not develop retinopathy of prematurity.

Results: The mean birth week of the babies was 30.1±0.24 weeks (23-36 weeks), and the mean birth weight was 1362.3±378.6 grams (450-2020 grams). Retinopathy of prematurity at different stages was detected in 21 (16.2%) of 130 patients. Eight (6.1%) of all patients screened for retinopathy of prematurity required treatment. Intravitreal ranibizumab was administered to seven patients (5.3%) with Stage III retinopathy, and both ranibizumab and laser therapy were applied to one patient with Stage IV retinopathy. Week of birth and low birth weight ($p<0.001$), duration of oxygen therapy ($p<0.001$), receiving surfactant treatment ($p=0.002$), sepsis ($p<0.001$), blood transfusion ($p<0.001$), intraventricular haemorrhage ($p=0.019$), apnea ($p<0.001$), anemia ($p<0.001$), hypoxia ($p<0.001$), acidosis ($p<0.001$) and low APGAR score ($p<0.001$) were found to significantly decrease the risk of developing retinopathy of prematurity.

Discussion and Conclusion: The development of retinopathy of prematurity can be reduced by appropriate management of risk factors that increase retinopathy of prematurity, such as low birth week and weight, high concentration and long-term oxygen use. Although there is no clear recommendation for the treatment of retinopathy of prematurity, it is thought that intravitreal ranibizumab treatment may be a good option in selected cases.

Keywords: Meonatal; ranibizumab; retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a physiopathological condition of unknown pathogenesis, characterized by retinal neovascularization, macular dragging and consequent retinal detachment in the developing retinas of premature infants with low birth weight[1]. ROP is the leading cause of childhood blindness worldwide, especially in developing countries[2]. Although the pathogenesis of ROP has not been fully elucidated, retinal damage develops as

Correspondence (İletişim): Baran Cengiz Arcagök, M.D. Acıbadem Mehmet Ali Aydınlar Universitesi Tip Fakultesi, Cocuk Sagligi ve Hastaliklari Anabilim Dali, Neonatoloji Bilim Dali, Istanbul, Turkey
Phone (Telefon): +90 505 627 22 09 **E-mail (E-posta):** baranarcagok@hotmail.com
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a result of first the cease of development of blood vessels in the retina due to hyperoxia, asphyxia, hypothermia, and acidosis, and then the onset of neovascularization with hypoxia as a result of impaired blood supply to the retina[3,4]. Early detection of retinal damage and appropriate treatment can prevent blindness in these infants. Especially in recent years, in parallel with the increase in the quality of newborn care with the developing technology, the chance of survival of babies with low birth weight and low birth week has increased, and ROP has become a more common problem[4]. In many studies, it has been found that both the development of ROP and the development of severe ROP increase proportionally with low birth week and low birth weight[5-7]. In this study, it was aimed to evaluate the incidence of ROP within three years in premature infants followed up in our clinic, to determine the risk factors that play a role in the development of ROP, and to evaluate the intravitreal ranibizumab (IVB) treatment and its results.

Materials and Methods

Infants who were hospitalized in our unit between April 2017 and April 2020, with a birth week of less than 32 weeks and/or a birth weight of less than 1500 grams, and babies with a birth week above 32 weeks and/or a birth weight of 1500 grams and who required cardiorespiratory support and were determined to be at risk of ROP by the clinician, were examined in terms of ROP development by the Department of Ophthalmology in line with the recommendations of the American Academy of Pediatrics. ROP examinations were performed in the Neonatal Intensive Care Unit (NICU) or in Ophthalmology Outpatient Clinic (for discharged infants), after dilating the eye pupils with 2.5% phenylephrine and 0.5% tropicamide. Ophthalmological examinations were repeated at regular intervals according to the severity of the retinopathy, using the follow-up program recommended by the American Academy of Pediatrics, until complete vascularization of the retina reached zone 3 (the most peripheral region of the temporal retina). Medical records of retinal examinations of preterm infants who met the screening criteria were evaluated retrospectively. The criteria for the treatment of ROP were determined according to the early treatment ROP (ETROP)[8]. According to the International Classification of Retinopathy of Prematurity, stages 1 to 2 were divided into 5 stages defined as mild ROP, and stages 3 to 5 as severe ROP. Those who needed treatment for ROP were also defined as severe ROP[9]. Risk factors including week of birth, birth weight, mode of delivery, gender, APGAR scores, need for mechanical ventilation, ≥40% oxygen therapy, duration of oxygen therapy, surfactant therapy, acidosis, hypoxia, sepsis, erythrocyte transfusion, intraventricular hemorrhage, apnea and anemia that may affect the development of ROP were compared in cases with and without ROP. Our study also investigated the need for laser photocoagulation, intravitreal ranibizumab (IVR), and vitreoretinal surgery for ROP.

Data were evaluated using IBM SPSS version 23.0 statistical package program and R version 4.0.0 software. Numerical variables in the study were expressed as mean, standard deviation, median, minimum and maximum values, and categorical variables were expressed in numbers and percentages. Comparisons of two independent groups for numerical variables were made using independent groups t-test for those who provided the normality assumption and the Mann-Whitney U test for those who did not. Comparisons between categorical variables were made using Pearson's Chi-square test, and Fisher's Exact Chi-square and Exact Chi-square tests were used when necessary. The relationships between the variables thought to affect the development of ROP were examined with the firth logistic regression model. As a result of the regression model, the odds ratio is presented together with the confidence interval of the odds ratio and the significance value of the model. $P<0.05$ was accepted as statistical significance level. Our study was approved by the ethics committee (Decision no: 2021-03/31). Informed consent was obtained from parents prior to initial ROP screening and treatment.

Results

The mean birth week of 130 premature babies screened to detect ROP in our clinic was 30.1±0.24 weeks (23-36 weeks), and the mean birth weight was 1362.3±378.6 grams (450-2020 grams). 72 of the patients included in the study were male and 58 were female. 93.1% of the patients were delivered by cesarean section. The descriptive characteristics of the patients are shown in Table 1.

Of the 130 patients evaluated, 21 had ROP at different stages [n=12 Stage I (9.2%); n=2 Stage II (1.4%); n=6 Stage III (3%); n=1 Stage IV (0.7%)], and severe ROP was detected in 8 of them. The birth week of 66.7% of babies with ROP was ≤27 weeks, and 33.3% of them were between 28-31 weeks. ROP was not detected in any infant above ≥32 birth weeks. The birth week of 87.5% of babies with severe ROP was ≤27 weeks. A statistically significant correlation was found between the detection status of ROP and the severity of ROP and the week of birth ($p<0.001$). Birth weight of 81% of infants with ROP

Table 1. Descriptive characteristics of patients

	n	%
Gender		
Female	58	44.6
Male	72	55.4
Birth Week		
≤27 weeks	17	13.1
28-31 weeks	79	60.8
32-33 weeks	29	22.3
≥34 weeks	5	3.8
Birth Week		
Mean±Standard Deviation	30.1±2.24	
Minimum-Maximum	23-36	
Median (1. Quartile -3. Quartile)	30.0 (28.0-32.0)	
Birth Weight		
≤1000 gr	27	20.8
1001-1250 gr	24	18.5
1251-1500 gr	29	22.3
>1500 gr	50	38.5
Birth Weight		
Mean±Standard Deviation	1362.6±378.6	
Minimum-Maximum	450-2020	
Median (1. Quartile -3. Quartile)	1400.0 (1088.7-1680.0)	
Mode of Delivery		
Normal	9	6.9
Cesarean	121	93.1

n: Number.

was ≤1000 grams. ROP was not detected in any patient with a birth weight of >1250 grams. The birth weight of all babies with severe ROP was <1000 grams. A statistically significant correlation was found between the presence status of ROP and the severity of ROP and birth weight (p<0.001).

Of all patients screened for ROP, 8 required treatment. IVR was applied to 7 patients with Stage III ROP, and ranibizumab and laser therapy were applied to 1 patient with Stage IV ROP. Low birth weight and gestational age, high concentration of oxygen therapy, sepsis, blood transfusion, intraventricular hemorrhage (IVH), apnea, anemia, hypoxia and acidosis were found to be associated with the development of ROP. Comparison of risk factors for ROP is shown in Table 2. The relationships between the variables thought to affect the development of ROP were examined with the univariate firth logistic regression model (Table 3).

Accordingly, it was determined that the week of birth and low birth weight (p<0.001), the duration of oxygen therapy (p<0.001), the presence of surfactant treatment (p=0.002), sepsis (p<0.001), blood transfusion (p<0.001), IVH (p=0.019), apnea (p<0.001), anemia (p<0.001), hypoxia (p<0.001), acidosis (p<0.001) and low APGAR score (p<0.001) were found to significantly increase the risk of developing ROP.

Discussion

In our clinic, we found the incidence of ROP to be 16.2% during a three-year follow-up, in infants with a birth weight of less than 32 weeks and/or birth weight of less than 1500 g, and infants with a birth weight of over 32 weeks and/or birth weight of over 1500 g, who required cardiorespiratory support and determined to be at risk of ROP by the clinician. Our ROP frequency was found to be lower when compared to the results reported from countries that applied similar screening protocols in the literature[6,10-12].

The most effective risk factors in the development of ROP are low birth weight and gestational week[4]. In a multicenter study, cryotherapy for ROP (CRYO-ROP), which included 4099 infants with a birth weight of ≤1250 g, low birth weight and gestational week were found to be associated with ROP[13]. In subsequent studies, it was found that low

Table 2. Comparison of risk factors for ROP in infants with and without retinopathy

	ROP					Severe ROP				
	Absent		Present			Absent		Present		
	n	%[1]	n	%[1]	p	n	%[1]	n	%[1]	p
Birth Week										
≤27 weeks	14	66.7	3	2.8	<0.001[a]	7	87.5	10	8.2	<0.001[a]
28-31 weeks	7	33.3	72	66.1		1	12.5	78	63.9	
32-33 weeks	-	-	29	26.6		-	-	29	23.8	
≥34 weeks	-	-	5	4.6		-	-	5	4.1	
Birth Weight										
≤1000 gr	17	81.0	10	9.2	<0.001[a]	8	100.0	19	15.6	<0.001[a]
1001-1250 gr	4	19.0	20	18.3		-	-	24	19.7	
1251-1500 gr	-	-	29	26.6		-	-	29	23.8	
>1500 gr	-	-	50	45.9		-	-	50	41.0	
Gender										
Female	11	52.4	47	43.1	0.434[b]	4	50.0	54	44.3	1.000[c]
Male	10	47.6	62	56.9		4	50.0	68	55.7	
Mode of Delivery										
Normal	-	-	9	8.3	0.353[c]	-	-	9	7.4	1.000[c]
Cesarean	21	100.0	100	91.7		8	100.0	113	92.6	
≥%40 Oksigen										
Present	21	100.0	3	2.8	<0.001[a]	8	100.0	16	13.1	<0.001[a]
Absent	-	-	106	97.2		-	-	106	86.9	
Mechanical Ventilation										
Present	21	100.0	90	83.3	0.034[a]	8	100.0	103	85.1	0.372[a]
Absent	-	-	18	16.7		-	-	18	14.9	
Surfactant treatment										
Present	21	100.0	79	72.5	0.003[a]	8	100.0	92	75.4	0.197[a]
Absent	-	-	30	27.5		-	-	30	24.6	
Sepsis										
Present	17	81.0	16	14.7	<0.001[b]	8	100.0	25	20.5	<0.001[a]
Absent	4	19.0	93	85.3		-	-	97	79.5	
Blood transfusion										
Present	21	100.0	25	22.9	<0.001[b]	8	100.0	38	31.1	<0.001[a]
Absent	-	-	84	77.1		-	-	84	68.9	
Intraventricular Haemorrhage										
Present	5	23.8	7	6.4	0.025[a]	4	50.0	8	6.6	0.002[a]
Absent	16	76.2	102	93.6		4	50.0	114	93.4	
Apnea										
Present	21	100.0	20	18.3	<0.001[b]	8	100.0	33	27.0	<0.001[a]
Absent	-	-	89	81.7		-	-	89	73.0	
Anemi										
Present	21	100.0	21	19.3	<0.001[b]	8	100.0	34	27.9	<0.001[a]
Absent	-	-	88	80.7		-	-	88	72.1	
Hypoxia										
Present	15	71.4	-	-	<0.001[a]	8	100.0	7	5.7	<0.001[a]
Absent	6	28.6	109	100.0		-	-	115	94.3	
Acidosis										
Present	14	70.0	-	-	<0.001[a]	7	100.0	7	5.7	<0.001[a]
Absent	6	30.0	109	100.0		-	-	115	94.3	

n: Number; [1]: Column percentage; [a]: Fisher's Exact chi-square test; [b]: Pearson chi-square test; [c]: Fisher's exact test; ROP: Retinopathy of prematurity.

Table 3. Logistic regression analysis results between variables and ROP development

	ROP		
	OR	**95% CI**	**p**
Gender			
Female	1		0.435[a]
Male	0.69	0.27-1.74	
Birth week	0.21	0.09-0.39	<0.001[a]
Birth weight	0.992	0.987-0.995	<0.001[a]
Mode of delivery			
Normal	1		0.243[a]
Cesarean	4.06	0.48-531.34	
Oxygen treatment duration	1.05	1.03-1.08	<0.001[a]
Mechanical ventilation			
Present	2.46	0.77-10.08	0.128[a]
Absent	1		
Surfactant treatment			
Present	16.49	2.15-2120.33	0.002[a]
Absent	1		
Sepsis			
Present	22.03	7.42-78.85	<0.001[a]
Absent	1		
Blood transfusion			
Present	142.49	18.50-18341.79	<0.001[a]
Absent	1		
Intraventricular Haemorrhage			
Present	4.55	1.29-15.40	0.019[a]
Absent	1		
Apnea			
Present	187.73	24.12-24219.70	<0.001[a]
Absent	1		
Anemia			
Present	176.99	22.80-22822.68	<0.001[a]
Absent	1		
Hypoxia			
Present	522.23	59.23-69484.22	<0.001[a]
Absent	1		
Acidosis			
Present	488.53	54.92-65071.55	<0.001[a]
Absent	1		

[1]: Column percentage; [a]: The likelihood-ratio statistics obtained in Firth logistic regression; ROP: Retinopathy of prematurity; CI: Confidence interval.

birth week and birth weight were associated with both the development of ROP and the need for treatment[14-17]. In our case group, a significant relationship was found between the development of ROP and babies with lower birth weight and earlier gestational weeks, parallel to the literature. Each weekly increase in the birth week of babies increased the probability of developing ROP by 79% (OR: 0.21, 95% CI, 0.09-0.39; Table 3), and each gram increase in birth weights increased the probability of developing ROP by 1% (OR: 0.992, 95% CI, 0.987-0.995; Table 3).

Oxygen therapy is known to increase the risk of developing ROP[4]. Supplemental oxygen use, oxygen concentration, and duration of oxygen use are among the most frequently identified risk factors for severe ROP and ROP that requires treatment[4,18]. Many studies have found that the duration of oxygen therapy increases the

risk of developing severe ROP[19-21]. In this study, similar to other studies, it was found that the duration of oxygen therapy increased the risk of developing ROP, and a statistically significant relationship was found between exposure to high concentrations of oxygen and the development of ROP. Each daily increase in the duration of oxygen use increased the risk of ROP 1.05 times (OR:1.05, 95% CI, 1.03-1.08; Table 3).

Hemoglobin concentrations decrease and anemia of prematurity develops in premature infants due to frequent postnatal blood tests and insufficient erythropoiesis[22]. Both anemia and erythrocyte transfusions for the treatment of anemia are known risk factors for the development of ROP[23]. In the study of Hengartner et al.[24], they found that multiple blood transfusions were associated with the development of advanced ROP. Zhu et al.[25] revealed in their meta-analysis that erythrocyte transfusions were an independent risk factor for the development of ROP, especially in small premature infants. In our study, similar to previous studies, we found that there was a significant relationship between anemia and erythrocyte transfusion and the development of ROP, and that they increased the risk of ROP. Therefore, we think that the development of ROP may decrease with the use of restrictive transfusion guidelines and the restriction of the number of transfusions, especially when making blood transfusion decisions in small premature infants.

Neonatal sepsis is among the most commonly identified risk factors for ROP at any stage and for severe ROP[4,17]. Many studies have found a close relationship between the development of ROP and sepsis[14,26]. According to the meta-analysis results of Wang et al.[27], it was determined that sepsis increased the development of ROP and severe ROP. In this study, in parallel with the results of other studies, we found that there was a significant relationship between sepsis and the development of ROP, and we found that the risk of developing ROP increased in babies with sepsis.

According to the results of several studies, acidosis has also been shown to increase the risk of developing ROP[28,29]. In the study of Extremely Low Gestational Age Newborns, 29 researchers thought that preterm babies with blood gas disorders in two of the first three days of life might be at risk of severe ROP, and based on this hypothesis, they concluded that repeated low pH in the first three days was associated with an increased risk of severe ROP[30]. In our study, we found acidosis in 70% of infants who developed ROP. Similar to the results of other studies, we found a significant relationship between acidosis and the development of ROP.

The most important approach in the management of ROP is to try to prevent the development of retinopathy by improving prenatal and perinatal care. However, considering that severe ROP cannot be completely prevented, therapeutic interventions are required. Conventional laser therapy and intravitreal injection of anti-VEGF agents (bevacizumab, ranibizumab) to inhibit intravitreal angiogenesis are most commonly used in the treatment of ROP[4,31]. Although intravitreal bevacizumab therapy has been shown to have significant benefits in type 1 ROP compared to conventional laser therapy, there is not enough evidence for it to be used alone as a first-line treatment[32]. In our clinic, due to complications such as severe narrowing of the visual field and late complications such as myopia and cataracts with ablation of a very large retinal area with laser treatment in babies with Zone 1 ROP, 2 patients who developed Zone 2 Stage 3 ROP and five patients who developed Zone 1 Stage 3 ROP received intravitreal ranizibumab treatment without any problems and no complications were encountered. An additional second dose of intravitreal ranizibumab was administered to two patients 16 and 20 days later, respectively.

Conclusion

As a result, there are currently no safe interventions supported by high-quality evidence to prevent severe ROP. The development of ROP can be reduced by appropriate management of risk factors that increase the risk of development of ROP, such as low birth week and weight, high concentration and long-term oxygen use. Although there is no definite recommendation regarding the routine use of intravitreal ranizibumab in terms of its efficacy and safety in the treatment of ROP, it is thought to be a good treatment option in selected cases where laser treatment is inconvenient or not applicable.

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