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Original Article

Risk factors, incidence, and long-term outcomes of premature infants with retinopathy in a single tertiary clinic

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Abstract

Objective: This study aims to evaluate the risk factors of patients with retinopathy of prematurity (ROP) in a single tertiary clinic and to present the long-term refractive results of the patients who were treated.

Methods: Premature infants referred to Yeni Yüzyıl University Hospital or followed in the Neonatal Intensive Care Unit (NICU) of Yeni Yüzyıl University Hospital between 2017 and 2020 were evaluated retrospectively. In this study, patients were evaluated in three groups according to their gestational weeks (<28 gw, 29-32 gw, >32 gw). According to the Early Treatment Retinopathy Cooperative Group (ETROP) study, treatment was recommended for infants with Type 1 ROP. Spherical equivalent (SEQ), cylindrical and spherical values of the treated cases were recorded at all follow-ups.

Results: A total of 646 premature babies born before 38 weeks were recorded between 2017 and 2020. A hundred two infants (15.7%) in group 1, 320 infants (49.53%) in group 2, and 224 infants (34.6%) in group 3 were examined. Among all infants, 18 eyes (1.39%) of 9 infants were treated with only one intravitreal injection of bevacizumab (0.025 ml/0.625 mg). The mean SE and spherical values decreased over time at the 3rd, 6th, and 12th month follow-ups.

Conclusion: ROP can be controlled with appropriate and effective treatment. Intravitreal injection of bevacizumab is a highly effective treatment option for type 1 ROP disease and Aggressive Posterior ROP. Long-term studies involving more patients are needed to evaluate the effect of treatment options on the refractive outcome.

Keywords: Bevacizumab, refractive result, retinopathy of prematurity.

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INTRODUCTION

Premature retinopathy is a proliferative vascular disease in premature infants and firstly named as retrolental fibroplasia in 1954 by Reese et al (1). In 1984, The International Classification of Retinopathy of Prematurity (ICROP) was created by specialists from 11 countries (2). In the following years, screening and treatment options were revised with the contributions of other multicenter studies after this first guideline. The major risk factors for this preventable childhood blindness are low gestational age and oxygen therapy. In developing countries, there is not enough skilled equipment or specialists to care for premature infants (3). Thus, screening programs for the evaluation of early retinopathy of prematurity (ROP) can be updated due to the latest socio-economic conditions in developing countries such as our country. According to the most comprehensive study conducted in Turkey, the recently updated ROP screening program, also recommends screening infants born <1700 g or ≤34 weeks to capture all infants requiring treatment (3,4). It is remarkable that screening should be done with more aggressive criteria in our country compared to developed countries.

This study aims to examine the incidence of ROP, evaluate the risk factors, and present the long-term results of preterm requiring treatment among preterm who applied to the clinic for screening and followed up in the intensive care unit.

MATERIALS AND METHODS

The findings in premature babies who were referred to the ROP clinic to Yeni Yüzyıl University hospital for examination and infants who followed up and fit the including criteria in the Neonatal Intensive Care Unit (NICU) between 2017 and 2020 were evaluated retrospectively. Informed consent forms were obtained from first-degree relatives. Ethical committee approval was obtained from the Clinical Research Ethical Committee of Yeni Yüzyıl University Gaziosmanpasa Hospital. (Approval number: 04.03.2021/8). The study was a retrospective and observational clinical case series. A total of 646 infants with gestational age (GA) ≤37 weeks and undergoing ROP screening in the center participated in the study. The results of the ROP screening examinations, the clinical characteristics of the infants, and the treatment outcomes of the treated were analyzed. Infants who were followed up after the first screening and whose examinations were completed were included in the study. Clinical risk factors can be classified as antenatal, natal, and postnatal. The higher natal risk factors are lower birth weight and gestational age for developing ROP disease. Several postnatal risk factors of ROP can be listed, especially for infants in the NICU. The most important ones include supplemental oxygen usage, apnea, mechanical ventilation, sepsis, intraventricular hemorrhage, anemia, thrombocytopenia, and less weight gain (5-7). In the current study, we investigated risk factors listed in table 1 as gestational age, birth weight, maternal age, sepsis, respiratory distress syndrome, invasive ventilation, non-invasive ventilation, intracranial hemorrhage, and bronchopulmonary dysplasia. The first ROP examination of all premature born with >30 GA was performed 4 weeks after birth. However, since there was a risk of severe ROP in babies born at ≤30 GA, the first examination was performed within 2-3 weeks after birth. Ophthalmic examinations continued until vascularization was completed for all infants. The timing of the initial examination and subsequent follow-up screening was scheduled according to the recommendations of the American Academy of Ophthalmology, the American Academy of Pediatrics, and the American Society of Pediatric Ophthalmology and Strabismus (8). For pupil dilation, 0.5% tropicamide and 2.5% phenylephrine eye drops were instilled three times at 5-minute intervals one hour before the eye examination. The screening was performed by a single physician (OBC) by aid of a +28 D lens under topical anesthesia using a speculum and a depressor. Patients' findings were recorded according to the criteria determined by the International Classification of Retinopathy of Prematurity (ICROP) (9). To report the anteroposterior location of the lesion, three concentric area have been described as 'Zone' description. The 'Stage' definition was used to describe the abnormality and severity of the vascular response, and the circumferential extent of each sector and stage was recorded at each

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examination. Also, the presence of 'plus disease' or 'preplus disease' was noted. According to the Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP) trial, treatment was offered to the Type 1 ROP group. The inclusion criteria for Type 1 ROP were Zone I or II, any Stage with plus disease, or Zone I, Stage 3 ROP without the plus disease. Aggressive Posterior ROP (APROP) described as at least 2 quadrants of vascular tortuosity and dilatation in any zone was also treated immediately (9). Premature babies were divided into three groups. Group 1 was included at ≤ 28 weeks, group 2 between 29-32 weeks, and group 3 between 32-37 weeks. All recorded risk factors and patient findings were analyzed retrospectively. Intravitreal bevacizumab (IVB) injection was preferred as the initial treatment. After povidone-iodine application, intravitreal injections were made under topical anesthesia. Bevacizumab injections (0.025 ml/0.625 mg) were performed with a 30-gauge needle at 1.5 mm from the limbus. The patients were checked on the 1st day, 3rd day, and 1st week postoperatively. Cases showing signs of regression were recorded and these findings were accepted as a reduction in vessel dilatation and tortuosity, involution of tunica vasculosa lentis, decrease in vitreous haze and resolution of intraretinal hemorrhages. All injected cases were checked at intervals determined according to their findings. Refractive errors of injected infants were determined three times 3-6-12 months after injections, 30 minutes after administration of 0.5% tropicamide/0.5% phenylephrine with the aid of a Welch Allyn SureSight (WASS; Welch Allyn, Skaneateles Falls, New York) hand-held autorefractor. In case of inconsistency between these measurements, consecutive measurements were repeated according to the concordant one and the average of the three measurements was evaluated at the end. The SE value was accepted by adding spherical value and half of the cylindrical value.

Table 1. Distribution of risk factors and clinical features between Groups (according to Gestational Age)

	Group 1 (≤28 GA) (n=102)	Group 2 (29-32 GA) (n=320)	Group 3 (≥32 GA) (n=224)
Gestational Age (Weeks, mean ± SD) (Min-max)	26 ± 2.1 (24-28)	30 ± 1.3 (29-32)	34,7 ± 2.5 (32-37)
Birth Weight (g, mean ± SD) (Min-max)	1024±105 (850-1204)	1404±400 (1240-1850)	1850±646 (1600-2450)
Maternal Age (y, mean ± SD)	32 ± 4.3	34 ± 3.8	36 ± 2.4
Female/ Male (n)	45/57	206/114	114/110
Sepsis (n) (%)	46 (45.09 %)	98 (30.62 %)	67 (29.91%)
RDS (n) (%)	35 (34.31 %)	79 (24.68 %)	45 (20.08 %)
Invasive Ventilation (n) (%)	49 (48.03 %)	75 (23.43 %)	23 (10.26 %)
Invasive Ventilation (days± SD)	57 ± 13.4	24 ± 2.2	12 ± 1.5
Noninvasive Ventilation (n) (%)	32 (31.3 %)	68 (21.25 %)	14 (6.25 %)
Noninvasive Ventilation (days± SD)	45 ± 3.34	22 ± 2.1	10 ± 1.7
Intracranial hemorrhage (n) (%)	12 (11.76 %)	10 (3.12 %)	5 (2.23 %)
BPD (n) (%)	35 (34.31 %)	54 (16.87 %)	10 (4.46 %)
Any Stage ROP occurrence (n) (%)	68 (66.6%)	175 (54.6%)	25 (11.1 %)
Treatment requirement (n) (%)	5 (4.9 %)	3 (0.93 %)	1 (0.44 %)

GA: Gestational Age, RDS: Respiratory Distress Syndrome, BPD: Bronchopulmonary Dysplasia

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Statistical Analysis

Statistical analyses were performed using the SPSS Software version 22 (SPSS for Windows, SPSS Inc., Chicago, IL, USA). The variable was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov test) to determine whether they are normally distributed. Descriptive analyses were presented using medians and interquartile ranges for the non-normally distributed and ordinal variables. Friedman tests were conducted to test whether there is a significant change between refractive outcomes at the 3rd, 6th, and 12th months. Paired Student's t-test was used to compare the measurements at two-time points for each refractive outcome. A p-value of less than 0.05 was considered to show a statistically significant result.

Table 2. Clinical features of treated infants.

Case	GA (weeks)	Eye (R/L)	Gender	Birth Weight (g)	Stage/ Zone/Plus ±/ APROP±	Time of treatment (weeks)	Complication	Recurrence
Case 1	28	R	F	952	Stage 3/Zone 1/ Plus-/ Aprop -	31	None	None
	28	L	F	952	Stage 3/Zone 1/ Plus -/ Aprop -	31	None	None
Case 2	27	R	M	875	Stage 3/Zone 2/ Plus-/ Aprop -	30	None	None
	27	L	M	875	Stage 3/Zone 1/ Plus+/ Aprop +	30	None	None
Case 3	29	R	F	960	Stage 3/Zone 1/ Plus+/ Aprop +	31	Air bubble in vitreous	None
	29	L	F	960	Stage 3/Zone 1/ Plus+/ Aprop +	31	None	None
Case 4	29	R	M	1120	Stage 3/Zone 1/ Plus+/ Aprop +	31	Subconj. Hemorrhage	None
	29	L	M	1120	Stage 3/Zone 1/ Plus+/ Aprop +	31	Subconj. Hemorrhage	None
Case 5	31	R	F	1285	Stage 3/Zone 1/ Plus+/ Aprop +	35	None	None
	31	L	F	1285	Stage 3/Zone 1/ Plus+/ Aprop +	35	None	None
Case 6	28	R	M	945	Stage 3/Zone 1/ Plus+/ Aprop +	30	None	None
	28	L	M	945	Stage 3/Zone 1/ Plus+/ Aprop +	30	None	None
Case 7	30	R	F	1290	Stage 3/Zone 2/ Plus +/ Aprop -	34	None	None
	30	L	F	1290	Stage 3/Zone 2/ Plus+/ Aprop -	34	None	None
Case 8	32	R	M	1640	Stage 3/Zone 2/ Plus+/ Aprop +	36	None	None
	32	L	M	1640	Stage 3/Zone 2/ Plus+/ Aprop +	36	None	None
Case 9	31	R	F	1370	Stage 3/Zone 1/ Plus+/ Aprop +	35	Subconj. Hemorrhage	None
	31	L	F	1370	Stage 3/Zone 1/ Plus+/ Aprop +	35	Subconj. Hemorrhage	None

F: female; M: male; Subconj Hemorrhage: subconjunctival hemorrhage.

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RESULTS

A total of 646 premature infants born before 38 weeks were recorded between 2017 and 2020. Demographical features of patients who were divided into three groups according to gestational age are shown in Table 1. A hundred two infants (15.7%) in group 1, 320 infants in group 2 (49.53%), and 224 infants (34.6%) in group 3 were examined. Among all infants, 18 eyes of 9 infants (1.39%) were treated with only one intravitreal injection of bevacizumab. No further treatment was required for all treated patients. The frequency of ROP requiring treatment was 4.9% in group 1 infants, 0.93% in group 2 and 0.44% in group 3. Treated infants' clinical features are shown in Table 2. At the time of the first diagnosis, 13 eyes were diagnosed with APROP, and treatment was performed within 24-48 hours. Regarding post-injection side effects, subconjunctival hemorrhage in both eyes of two patients (Case 4 and Case 9) and an air bubble in the vitreous of one patient (Case 3) were detected. Regression in tortuosity and dilatation was observed within 3 days in each case after the injection. In the follow-ups, it was observed that the total retinal maturation was completed in all patients included in the study and no pathologies such as macular traction, retinal detachment and recurrence were detected in the treated patients. The mean post-conceptual age at injection was 32.3 ± 2.3 weeks. The 3rd, 6th and 12th month refraction results of the treated patients who are still followed up were analyzed and refractive error outcomes of 18 eyes of 9 patients in the follow-ups are shown in Table 3. There was a statistically significant difference between all groups ($p<0.05$), and only the cylindrical values at the third and sixth months were not statistically significant (-1.38 ± 1.25 vs -1.06 ± 0.37, $p=0.081$, respectively). The mean SE and spherical values decreased over time at the 3rd, 6th, and 12th month follow-ups.

Table 3. Mean refractive error outcomes of treated patients (18 eyes of 9 patients) at follow-ups.

Refractive Errors	3-month follow-up (Mean±SD)	6-month follow-up (Mean±SD)	12-month follow-up (Mean±SD)	p*	p**	p***	p^a
SE, D	2.41 ± 0.73	1.63 ± 0.52	0.15 ± 1.03	**<0.001**	**<0.001**	**0.004**	**<0.001**
Spherical, D	3.11 ± 0.88	2.16 ± 0.62	0.33 ± 1.11	**<0.001**	**<0.001**	**0.001**	**<0.001**
Cylindrical, D	-1.38 ± -1.25	-1.06 ± 0.37	-0.36 ± 0.48	0.081	**0.01**	**0.009**	**0.007**

SE; spherical equivalent, D; diopter, SD; standard deviation
*p*value between the results at 3-month and 6-month follow-ups using paired sample t-test.*
*p** value between the results at 3-month and 12- month follow-ups using paired sample t-test.*
*p*** value between the results at 6-month and 12- month follow-ups using paired sample t-test.*
p^a value between the results of all three follow-ups using the Friedman test.

DISCUSSION

ROP is a serious preventable cause of blindness, especially in low-income countries, whose incidence and severity increase with the decrease in gestational age and birth weight. Although studies conducted in high-income countries have shown that the risk of developing ROP decreases for babies born at ≥32 weeks (10), the TR-ROP study in our country has shown that the risk of severe ROP continues in more mature preterm with a higher birth weight (3). The incidence of ROP varies by country. One of the most comprehensive studies, Early Treatment of Retinopathy of Prematurity (ETROP) Cooperative Group, reported that the incidence of ROP was 89% in infants whose gestational age did not exceed 27 weeks, 51.7% in infants between 28-31 weeks, and 14.2% in gestational weeks of at least 32 weeks (11). In the TR-ROP study, which is the most comprehensive multicenter

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study recently conducted in Turkey, the incidence of retinopathy in infants ≤28 weeks of age was reported as 62.9%. The incidence of ROP in infants with a gestational age of 28-32 weeks and a gestational age of at least 32 weeks was found to be 19.4% and 10.2%, respectively (3). These results are similar to the results of the current study. However, in our study, the incidence of ROP was 54.6% in infants whose gestational age was between 28 and 32 weeks and was higher than in other studies from Turkey (12-14). Sarıkabadayı et al. prospectively evaluated 700 infants with a birth weight of less than 2000 gr and GA of before 34 weeks, any stage of ROP was detected in 229 infants (32.7%), and 22 infants (9.6% of the whole cohort) required treatment (15). In the current study, although the number of cases was similar, infants born at elder gestational age (<38 weeks) were included and the incidence of ROP cases with required treatment was 1.39%, and the frequency of ROP for any stage was 41.1%. Akman et al. reported a ROP analysis of 801 infants whose gestational age was less than 37 weeks retrospectively (16). They divided the infants into three groups based on their gestational age. Those with GA less than 32 weeks were defined as group 1, 32-34 weeks as group 2, and over 34 weeks as group 3. Risk factors (duration of oxygen supply and ventilation, bronchopulmonary dysplasia, sepsis) were analyzed as in the current study. Similarly, to our study, ROP was more common in infants with low gestational age, low birth weight, sepsis, BPD, sepsis, prolonged oxygen supply, and ventilator therapy. In the current study, only 1.39% of infants screened for ROP received treatment and intravitreal bevacizumab injection was performed as the first-line treatment. Laser photocoagulation is still the gold standard in the treatment of retinopathy of prematurity. However, there are situations where laser therapy is contraindicated in conditions such as poor pupil dilation, vitreous clouding or bleeding, and rubeosis iridis (17). In addition, in the literature, it is reported that the success rate of laser photocoagulation is lower in cases with zone 1 ROP than in cases with zone 2 ROP, and laser photocoagulation therapy has been shown to cause severe visual field loss in patients with zone 1 ROP (18). Anti-vascular endothelial growth factor therapies are the most widely used treatment modalities recently. The 'Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study, a randomized multicenter study, analyzed the comparative efficacy and side effects of intravitreal bevacizumab monotherapy (IVB) (0.625 mg per 0.025 ml) and conventional laser therapy (19). Recurrence was less in the bevacizumab group than in the laser-treated group (4% vs 22%, respectively) No systemic or local toxic effects attributable to bevacizumab were observed, but the study concluded that the study population was too small and long-term results were needed to demonstrate the drug's safety. Although there are concerns about their potential systemic side effects, numerous studies have been conducted on the long-term systemic effects and possible side effects on peripheral retinal vascularization of the usage of different anti-VEGF agents in combination or monotherapy. In our country, Yetik et al. evaluated the long-term results (27 months) of IVB treatment in eyes with type 1 ROP, threshold disease, and APROP. The maximum number of injections was three and the success rates of one to three injections were 95.4%, 98.2%, and 100% respectively (20). In our study, 13 eyes had APROP and 5 of 18 eyes had type 1 ROP disease. After the first injection, an adequate regression was observed for all the patients and during the follow-up period, no recurrence was detected. Consistent with the literature, in our study, IVB monotherapy had a remarkable effect in the management of type 1 ROP and APROP. In the literature, the relationships related to the effect of ROP treatment management on refractive outcomes have been examined and different results have been reached. Kang et al. reported that there was no significant difference between intravitreal injection and laser treatment eyes in terms of spherical power, cylinder power and SEQ (21). In contrast to this research, the study in which the long-term (mean age of 2.5 years) refractive results of the BEAT ROP study group were analyzed, the mean refractive results of 211 eyes of 109 infants were evaluated after intravitreal injections and laser treatments. In this study, the prevalence of myopia after intravitreal bevacizumab injection was lower than in patients who received laser therapy (22). In a study conducted in our country, the postoperative 18th-month refractive results of patients who underwent intravitreal ranibizumab injection, intravitreal bevacizumab injection and laser therapy were examined. Myopic

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SE was detected in all three groups without statistical difference (23). In the current study, the mean SE decreased during the follow-ups and none of them had the trend of higher myopia.

Limitations: However, our study has several limitations, such as the small sample size and the inability to compare the long-term outcomes of different anti-VEGF agents and doses.

CONCLUSION

ROP can be controlled by using effective treatment options. Conventional LFC is still the first line of treatment in ROP, but intravitreal bevacizumab injection may be an effective first-line treatment for type 1 ROP disease and APROP. There are many factors, especially prematurity, that affect refractive outcomes in infants with ROP. Long-term studies involving more patients are needed to evaluate the effect of treatment options on refractive outcomes.

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