ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Diagnosis and Follow-Up in Retinopathy of Prematurity: Seven-Year Experience of a Single Center Descriptive Research

Prematüre Retinopatisinde Tanı ve Takip: Tek Merkezde 7 Yıllık Deneyim Tanımlayıcı Araştırma

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Preliminary results of this study were presented as poster presentations at the Türkiye Ophthalmological Association 48th National Congress, November 5-9, 2014, Antalya, Türkiye, and at the Türkiye Ophthalmological Association Winter Meeting, January 22-24, 2016, Antalya, Türkiye and also as oral presentation at the 17th International Eastern Mediterranean Family Medicine Congress, May 10-13, 2018, Adana, Türkiye.

ABSTRACT Objective: To present the incidence and screening results of retinopathy of prematurity (ROP) in preterm infants who were followed-up and treated in Ordu University Training and Research Hospital. **Material and Methods:** Medical records of 1,995 babies who underwent screening for ROP between January 2014 and June 2021 were reviewed retrospectively. Of these infants, 1,853 patients with a gestational age (GA) of ≤37 weeks who completed all screening sessions were included. **Results:** Any stage ROP (157 Stage I, 87 Stage II, 19 Stage III, and 43 aggressive ROP) was detected in 306 (16.51%) infants. None of the patients developed Stage IV or V disease. The mean GA (30.30±2.69 weeks) and birth weight (BW) (1,508.20±501.06 g) were significantly lower in patients with ROP at any stage. The rates of ROP were 13.20% and 65.25% in infants with a GA of >28 weeks and ≤28 weeks, respectively. This rates were also 12.05% and 53.23% in patients with a BW of >1,250 g and ≤1,250 g, respectively. Small GA and low BW were significantly associated with the presence of ROP. Severe ROP requiring treatment was detected in 1.2% of infants with a BW of >1,500 g and in 0.5% of patients with a GA of >32 weeks. The disease was spontaneously regressed in 80.39% of patients. Sixty (19.61%) patients received treatment [45 with low dose intravitreal bevacizumab (IVB) injection and 15 with diode laser photocoagulation]. **Conclusion:** Small GA and low BW are the main risk factors for ROP development. Severe ROP requiring treatment may occur even in heavier babies. Meticulously managed regular screening program providing early diagnosis and treatment prevents Stage IV or V ROP. Additionally, low dose IVB injection seems to be effective in the treatment of aggressive ROP.

Keywords: Retinopathy of prematurity; bevacizumab; light coagulation

ÖZET Amaç: Bu çalışmanın amacı, Ordu Üniversitesi Eğitim ve Araştırma Hastanesinde takip ve tedavi edilen preterm infantlarda prematüre retinopatisi (PR) insidansını ve tarama sonuçlarını sunmaktır. **Gereç ve Yöntemler:** Ocak 2014-Haziran 2021 tarihleri arasında PR taraması yapılan 1.995 bebeğin tıbbi kayıtları retrospektif olarak incelendi. Bu hastalardan tüm tarama seanslarını tamamlayan, gebelik yaşı (GY) ≤37 hafta olan 1.853 hasta çalışmaya alındı. **Bulgular:** Toplam 306 (%16,51) infantta herhangi bir evre PR (157 Evre I, 87 Evre II, 19 Evre III ve 43 agresif PR) saptandı. Hiçbir hastada Evre IV veya V hastalık gelişmedi. Ortalama GY (30,30±2,69 hafta) ve doğum ağırlığı (DA) (1.508,20±501,06 g) herhangi bir evre PR olan hastalarda anlamlı olarak daha düşüktü. GY>28 hafta ve GY≤28 hafta olan bebeklerde, PR oranları sırasıyla %13,20 ve %65,25 idi. DA>1.250 g ve DA≤1.250 g olan hastalarda ise bu oranlar sırasıyla %12,05 ve %53,23 idi. Düşük GY ve DA, PR varlığı ile anlamlı olarak ilişkili idi. DA>1.500 g olan infantların %1,2'sinde, GY>32 hafta olan bebeklerin ise %0,5'inde tedavi gerektiren ciddi PR saptandı. Hastaların %80,39'unda hastalık kendiliğinden geriledi. Altmış (%19,61) hastaya tedavi [45'ine düşük doz intravitreal bevasizumab (IVB) enjeksiyonu ve 15'ine diyot lazer fotokoagülasyon] uygulandı. **Sonuç:** Küçük GY ve düşük DA, PR gelişimi için esas risk faktörleridir. Daha ağır bebeklerde dahi tedavi gerektiren şiddetli PR oluşabilir. Erken tanı ve tedaviye olanak sağlayan, titizlikle yürütülen düzenli tarama programı Evre IV veya V PR'yi engeller. Ayrıca agresif PR tedavisinde düşük doz IVB enjeksiyonunun etkili olduğu görülmektedir.

Anahtar Kelimeler: Prematüre retinopatisi; bevasizumab; ışık koagülasyonu

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Retinopathy of prematurity (ROP), one of the leading causes of childhood blindness, is a proliferative retinal vascular disorder that can be seen in preterm patients with a low birth weight (BW) and small gestational age (GA).[1,2] While babies lower than 1,000 g and smaller than 28 weeks have an increased risk for severe ROP in high-income countries, the disease may be seen even in infants up to 37 weeks of GA and up to 2,000 g of BW in developing countries.[3] Nowadays, developments in neonatal intensive care units (NICUs), technological improvements and advanced treatment choices result in increasing survival rates of preterm babies in developing areas.[4] Eventually, regular eye examinations of premature infants, timely screening and appropriate treatment are crucial to improve visual outcomes and to prevent childhood blindness.[5]

The screening program in preterm infants aims to prevent serious ROP-related complications and visual loss with early diagnosis and appropriate treatment. An international screening criteria for ROP was considered not to be entirely applicable in the developing world.[6] Neonatologists and ophthalmologists are recommended to adjust their country-specific screening guidelines.[4] Turkish Ophthalmological Association (TOA) and Turkish Neonatal Society (TNS) suggested that "all preterm babies smaller than 34 weeks or lower than 1,700 g and those bigger than 34 weeks and heavier than 1,700 g receiving cardiopulmonary support and who were considered as risky by the attending clinician should be examined", in the revised National Guideline on ROP in 2021. It was also stated in this guideline that "the quality of different NICUs may vary, therefore it would be appropriate for each unit to determine its own screening criteria for ROP through epidemiological studies on its own patients".[7] This study aimed to show our epidemiological results and to present the incidence and screening results of ROP in preterm infants who were followed-up and treated in our clinic.

MATERIAL AND METHODS

Medical records of 1,995 neonates screened for ROP in Training and Research Hospital of Ordu University, Department of Ophthalmology between January 2014 and June 2021 were reviewed retrospectively. Ordu University Clinical Research Ethics Committee approved the study protocol (approval number: 2021/193, approval date: 26.08.2021) and the study procedures were conducted in accordance with the tenets of Declaration of Helsinki. The exclusion criteria were as follows: a GA bigger than 37 weeks, additional ocular or systemic pathologies, congenital or chromosomal anomalies and discontinuation of follow-up. The study included 1,853 babies with a GA of 37 weeks or less who completed all screening sessions. The demographic characteristics, GA and BW of the patients, the presence of ROP, the severity of the disease, the type of the treatment, and complications of the therapy were recorded. Only one of both eyes, preferably the eye with most advanced ROP, was included in the study.

All fundus examinations were performed by the same experienced ophthalmologist (AU) with an indirect binocular ophthalmoscope using a 28-diopter lens following pupillary dilatation under topical anesthesia. After the insertion of eyelid speculum, a scleral indenter was used to evaluate the peripheral retina. Fundus examination was first performed at between 4 and 6 weeks of life. The revised version of International Classification of Retinopathy of Prematurity (ICROP3) was used for clarifying the zone and the stage of the disease.[8] ROP requiring treatment was defined as severe ROP. The patients were treated with intravitreal bevacizumab (IVB) injection (0.25 mg/0.01 mL) or diode laser photocoagulation (DLP) according to the Early Treatment for Retinopathy of Prematurity (ETROP) Study Group.[9] All babies were periodically followed up in the ROP unit until retinal vessels reached the temporal ora serrata. The patients who completed all screening sessions were referred to the pediatric ophthalmology section for detailed ophthalmologic evaluation.

STATISTICAL ANALYSIS

All data analyse were performed using the SPSS statistical software package, version 25.0 (SPSS Inc., Chicago, IL, USA). The normality of the data distribution was checked with the Kolmogorov-Smirnov test. Categorical variables were expressed as frequency and percentage. Mann-Whitney U test was used when evaluating nonparametric variables that

did not show a normal distribution between the 2 groups. A binary logistic regression analysis was used to examine the risk factors associated with ROP development. Statistically significance was accepted as a p value less than 0.05.

RESULTS

A total number of 6,354 screening sessions [range: 3.33±2.35 (1-21)] was performed in 1,853 infants who were included in the study. The demographics of all babies were given in Table 1. While 681 (36.8%) infants were consulted from the NICU of Ordu University, Training and Research Hospital, 817 (44.1%) patients were referred from other NICUs in Ordu and 355 (19.1) babies were brought from different provinces.

In the current study, 306 (16.51%) babies developed ROP in different stages and zones. Disease at any stage was detected in 11% of patients followed up in our NICU, in 17.1% of patients consulted from other NICUs in Ordu and in 25.6% of patients brought from other provinces.

The mean GA and BW of patients with any stage ROP were 30.30±2.69 (range: 22-35) weeks and 1508.20±501.06 (range: 550-3,400) g, respectively. The mean GA and BW of infants without ROP were 33.37±2.19 (range: 25-37) weeks and 2081.11±556.00 (range: 600-4,000) g, respectively. The mean GA and BW were significantly lower in patients with any stage ROP compared to babies without ROP ($p<0.001$ and $p<0.001$, respectively).

The distribution of patients with and without ROP according to GA and BW was given in Table 2. The rates of any stage ROP were 13.20% and 12.05% in patients with a GA of >28 weeks and BW of >1,250 g, respectively. That rates were also 65.25% and 53.23% in patients with a GA of ≤28 weeks and BW of ≤1,250 g, respectively.

The binary logistic regression analysis of risk factors for development of ROP showed that smaller GA and lower BW were associated with the presence of ROP, significantly, but there were no statistically significant relationship between multiple births or the type of NICUs and ROP development ($p<0.001$, $p=0.008$, $p=0.721$ and $p=1.041$, respectively).

TABLE 1: Demographics of the patients.

Variables	
Gender	
Female	858 (46.30%)
Male	995 (53.70%)
Single births	1,350 (72.86%)
Multiple births	503 (27.14%)
Twins	467 (25.20%)
Triplets	36 (1.94%)
Gestational age (weeks)	32.86±2.55 (22-37)
Birth weight (grams)	1,986.50±587.09 (550-4,000)
Retinopathy of prematurity	
(+)	306 (16.51%)
(-)	1,547 (83.49%)

Data are given as mean standard deviation for continuous variables and frequency (percent) for categorical variables.

TABLE 2: Distribution of cases with and without retinopathy of prematurity.

Variables	ROP (+)	ROP (-)	n
Gestational age (n, %)			
≤28 weeks	77 (65.25%)	41 (34.75%)	118
29-32 weeks	169 (27.52%)	445 (72.48%)	614
33-37 weeks	60 (5.35%)	1,061 (94.65%)	1121
Birth weight (n, %)			
≤1,250 g	107 (53.23%)	94 (46.77%)	201
1,250-1,500 g	59 (30.73%)	133 (69.27%)	192
>1,500 g	140 (9.59%)	1,320 (90.41%)	1,460

ROP: Retinopathy of prematurity.

Of the 306 infants developed ROP, 157 had Stage I disease, 87 had Stage II disease and 19 had Stage III disease. None of the patients developed Stage IV or Stage V ROP. In accordance with ICROP3, aggressive ROP (A-ROP) was detected in 43 (14.05%) patients. The distribution of stages of ROP according to the BW and GA were given in Figure 1 and Figure 2.

Management of patients with ROP according to the stages was given in Table 3. Spontaneous regression of the disease was observed in 246 (80.39%) babies and retinal vessels reached temporal ora serrata in all of these patients. The mean BW and GA of these infants were 30.68±2.53 (range: 22-35) weeks

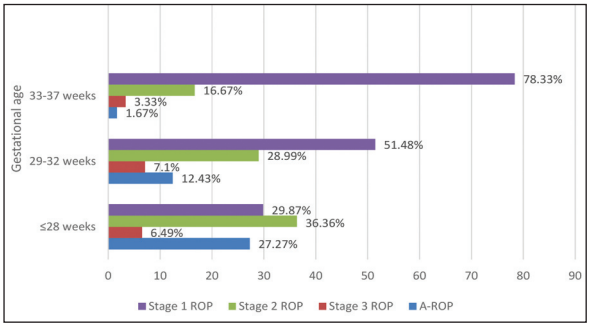

FIGURE 1: Distribution of stages of ROP according to the gestational age.

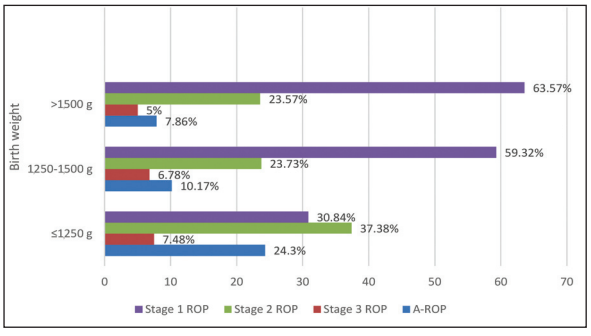

FIGURE 2: Distribution of stages of ROP according to the birth weight. Distribution of stages of ROP according to the birth weight.

and 1569.25±489.05 (range: 570-3,400) g, respectively. Severe ROP requiring treatment was detected in the remaining 60 (19.61%) infants with a mean GA of 28.77±2.83 (range: 24-34) weeks and BW of 1257.92±474.82 (range: 550-2,400) g. Patients with ROP requiring treatment had significantly lower mean GA and BW compared to infants whose disease regressed spontaneously ($p<0.001$ and $p<0.001$, respectively). Of the patients with severe disease, 45 (75%) received 0.25 mg/0.01 mL IVB injection. Despite IVB injection, A-ROP did not regress in one infant and this patient underwent a second IVB injection. Fifteen (25%) patients with severe ROP were treated with transpupillary DLP. Additional DLP was required in 2 patients because ROP did not regress despite DLP therapy. Nevertheless, secondary DLP was not required in any of the patients who received IVB injection. None of the patients required vitreoretinal surgery due to progressive disease in this study.

Retinal vessel development stopped at zone III in 1 patient who received IVB injection for A-ROP, and retinal vessels did not reach temporal ora serrata in this patient even though it was postmenstrual 70th weeks. Due to the small peripheral avascular area, no additional DLP was required and the baby was referred to the pediatric ophthalmology section for detailed ophthalmologic evaluation. Transient anterior segment inflammation in the early postoperative period occurred in 1 patient who received DLP for Stage III ROP, but resolved with topical corticosteroid and cycloplegic eye drops. One patient developed cataract and glaucoma following DLP and was referred to an advanced facility for treatment. Except for these 3 cases, there were no systemic or ocular side effects in any of the patients treated for ROP.

DISCUSSION

The rate of ROP is minimal in poorly-developed countries related to lower survival rates, and is also low in highly-developed countries including more advanced NICUs due to meticulously monitored oxygen supplementation and blood oxygen saturation.[10] However, the incidence of ROP in developing countries remains high related to insufficient awareness of risk factors of the disease and long-term oxygen therapy in order to increase the survival rates.[11,12] A recent multi-center study from Turkey (TR-ROP study) revealed that severe ROP may also occur in heavier and more mature babies in the developing countries.[12]

TABLE 3: Management of patients with retinopathy of prematurity according to the stages (n,%).

Stage	Intravitreal injection	Diode laser photocoagulation	Spontaneous regression	Total
Stage I ROP	0 (0%)	0 (0%)	157 (100%)	157
Stage II ROP	1 (1.2%)	1 (1.2%)	85 (97.6%)	87
Stage III ROP	1 (5.3%)	14 (73.7%)	4 (21%)	19
A-ROP	43 (100%)	0 (0%)	0 (0%)	43

ROP: Retinopathy of prematurity; A-ROP: Aggressive retinopathy of prematurity.

TR-ROP Study Group also suggested to set its own screening criteria for each unit, as there may be differences in the quality of different NICUs.[12]

Although the mean GA and BW of the patients in different NICUs were similar, the incidence of ROP (11%) was significantly lower in patients consulted from our NICU, in this study. This lower rate may reflect the difference of neonatal care in different NICUs. Similarly, TR-ROP Study Group reported significantly lower rates of severe ROP in the NICUs of university hospitals.[12] In our NICU, there was always a neonatologist over the course of the study. However, other NICUs in Ordu and other provinces were managed usually by consultant pediatricians. Better newborn care in university hospitals compared to non-university NICUs may result in lower incidence of ROP in our unit.

Previous reports from Turkey indicated that 19.6-36.3% of premature infants who underwent screening for ROP developed any stage disease.[5,13-15] The rate of severe ROP was also reported as 8-9.6% in previous studies from Turkey.[13,16] Reports from different countries (34.1% in Korea, 36.5% in Egypt, 37.8% in Taiwan, 44.5% in Brazil, 45% in Northern Iran) demonstrated a higher incidence of ROP at any stage.[17-21] A previous multi-center study from Turkey reported that 30% of babies developed any stage ROP, and 5% of the patients had severe ROP.[4] Later, TR-ROP study showed that 27% of infants developed ROP at any stage, and 6.7% of patients had severe ROP requiring treatment.[12] In this setting, any stage disease was detected in 16.51% of patients and 3.24% of all babies developed severe ROP requiring treatment. The lower incidence of severe ROP and any stage disease may be related to the higher number of patients with a GA of 33-37 weeks, in our study.

Different studies showed that infants larger than 32 weeks of GA and heavier than 1,500 g of BW may develop severe ROP requiring treatment.[4,12] The rates of severe ROP were 0.6% in babies with a BW of >1,500 g and 0.5% in infants with a GA of >32 weeks in a previous multi-center study from Turkey.[4] Similarly, TR-ROP study demonstrated severe ROP rates as 0.7% and 0.5% in babies heavier than 1,500 g and larger than 32 weeks, respectively.[12] Although the rate of severe ROP (0.5%) in our study was similar in infants with a GA of >32 weeks, this rate was higher in infants with a BW of >1,500 g (1.2%) compared to previous studies. Esen et al. reported higher rates of severe ROP in babies larger than 32 weeks (1.6%) and heavier than 1,500 g (2.9%).[16] Recently, TOA and TNS recommended that all preterm babies lower than 1,700 g or smaller than 34 weeks should be examined in the revised National Guideline on ROP in 2021.[7]

Previous studies demonstrated GA, BW and oxygen therapy as the main risk factors for ROP development.[5,12,13-15] Additionally, TR-ROP Study Group reported total days on oxygen supplementation, red blood cell transfusion, respiratory distress syndrome, respiratory support, sepsis, necrotizing enterocolitis, patent ductus arteriosus, intracranial haemorrhage, bronchopulmonary dysplasia and poor postnatal weight gain as other risk factors for the presence of ROP.[12] Anemia, hyperbilirubinemia, apnea, perinatal asphyxia were also presented as risk factors in previous studies.[5,13,14] In the binary logistic regression analysis, BW and GA were detected as risk factors for the development of ROP but risk factors other than GA, BW, multiple births and the types of NICU following the patient were not evaluated in our study.

The final results of ETROP trial showed the effectivity of laser retinal ablation therapy compared to conventionally managed fellow eye in patients with bilateral high-risk prethreshold ROP.[9] In our study, the disease completely regressed in patients who underwent DLP, consequently. Transient anterior segment inflammation occurred in one patient and also one infant developed glaucoma and cataract following DLP. Except for these 2 cases, no ocular side effects were observed in any of the patients who underwent DLP.

Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity Study demonstrated the efficacy of IVB monotherapy (0.625 mg/0.025 mL) in babies with Stage III+ROP in zone I disease.[22] Later studies investigated the lowest effective dose of IVB in premature infants due to concerns regarding its potential ocular and systemic side effects.[23-25]

Low dose (0.25 mg/0.01 mL) and conventional dose (0.625 mg/0.025 mL) IVB injection showed no difference in terms of short-term outcomes of ROP in zone I and II disease.[23] Accordingly, A-ROP was completely resolved in all patients following low dose (0.25 mg/0.01 mL) IVB injection in our study. There was also no ocular or systemic complications during or following IVB injection in this setting. Although a small persistent peripheral avascular area was detected at postmenstrual 70th weeks following IVB injection in only one patient, prophylactic DLP was not required. In the current study, none of the patients developed Stage IV or V disease requiring vitreoretinal surgery. This finding may be the result of regular screening program that provides early diagnosis and successful treatment in our ROP unit.

The lower incidence and treatment rates in this setting compared to previous studies may be related to the higher number of patients larger than 32 weeks of GA (61%) and heavier than 1,500 g of BW (79%). However, the higher rate of ROP requiring treatment (1.2%) in babies greater than 1,500 g is important in terms of drawing attention to the risk of severe ROP development in heavier babies. The lack of progressive disease requiring vitreoretinal surgery in our ROP unit may be the result of meticulously managed screening program, early diagnosis and appropriate therapy if needed. Furthermore, low dose (0.25 mg/0.01 mL) IVB injection was shown to be effective in the treatment of A-ROP.

There are also some limitations of our study. As a result of its retrospective design, we were unable to obtain some patients' medical records containing a detailed medical history. Consequently, risk factors other than low BW, GA, multiple births and the type of NICU could not be evaluated. Additionally, the number of patients treated with low dose IVB injection was also insufficient to evaluate the exact efficacy and safety profile of low dose IVB.

CONCLUSION

Ophthalmologists should be careful as severe ROP may develop even in heavier babies. The standardization of NICUs managed by neonatologists and actions to improve neonatal care quality can reduce the incidence of ROP. A regular screening program that provides early diagnosis and appropriate treatment may also prevent the development of Stage IV or V ROP requiring vitreoretinal surgery.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Aslıhan Uzun, Asena Keleş Şahin;* ***Design:*** *Asena Keleş Şahin;* ***Control/Supervision:*** *Aslıhan Uzun, Asena Keleş Şahin;* ***Data Collection and/or Processing:*** *Aslıhan Uzun;* ***Analysis and/or Interpretation:*** *Aslıhan Uzun, Asena Keleş Şahin;* ***Literature Review:*** *Aslıhan Uzun;* ***Writing the Article:*** *Aslıhan Uzun, Asena Keleş Şahin;* ***Critical Review:*** *Aslıhan Uzun, Asena Keleş Şahin;* ***References and Fundings:*** *Aslıhan Uzun;* ***Materials:*** *Aslıhan Uzun.*

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