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Klinik Araştırma

The Demographic and Clinical Characteristics of the Patients Treated for Type 1 Retinopathy of Prematurity

Prematüre Retinopatisi Nedeniyle Tedavi Edilen Hastaların Demografik ve Klinik Özellikleri

Hatice Bilge ARAZ ERŞAN*, Dilara PİRHAN, Sultan KAVUNCUOĞLU***, Nihat SAYIN****, Sadık Etka BAYRAMOĞLU****, Merih ÇETİNKAYA*******

**Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği, İstanbul*

***Kocaeli Üniversitesi Kocaeli TıpFakültesi, Göz Hastalıkları Kliniği, Kocaeli*

****Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Çocuk Hastalıkları Kliniği, İstanbul*

*****Kanuni Sultan Suleyman Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği, İstanbul*

******Kanuni Sultan Suleyman Eğitim ve Araştırma Hastanesi, Yenidoğan Kliniği, İstanbul*

ABSTRACT

Objective: *To present the demographic and clinical characteristics of patients who were treated for type 1 retinopathy of prematurity (ROP).*

Material and Method: *The medical records of 89 premature infants who were treated in the ophthalmology department of Kanuni Sultan Suleyman Education and Research Hospital between June 2012 and March 2014 and completed a 6-month-follow-up period were evaluated retrospectively. The patients were divided into two groups as inpatients and referrals.*

Results: *Seventeen infants were inpatients, and 72 infants were referrals. The mean gestational age (GA) and birth weight (BW) of the inpatients were significantly lower than those of referred infants (p=0.09 and p=0.024, respectively). The mean GA and BW of the inpatients with zone 1 ROPwere significantly lower than those of the referred infants (p=0.014 and p=0.048, respectively). There was no significant difference in postmenstrual age or chronological age at treatment between the inpatients and referred infants (p>0.05). No retinal detachment was observed.*

Conclusion: *The timely application of current treatment methods is successful in resolving severe ROP. The significantly higher mean BW and GA of the referred patients compared with the inpatient infants imply that patient outcomes at level 3 referral centers may not be representative of other neonatal intensive care units.*

Keywords: *retinopathy of prematurity, diode laser photocoagulation, intravitreal bevacizumab injection, developing country*

ÖZ

Amaç: *Tip1 prematüre retinopatisi (ROP) tanısıyla tedavi edilen hastaların demografik ve klinik özelliklerini ortaya koymak.*

Gereç ve Yöntem: *Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği'nde Haziran 2012 ve Mart 2014 tarihleri arasında tedavi gören ve en az 6 ay takipedilen, 89 preterm bebeği dosyaları retrospektif olarak tarandı. Hastalar yatan hastalar ve sevk edilen hastalar olmak üzere iki gruba ayrıldılar.*

Bulgular: *Tedavi edilen hastaların 17'si yatan, 72'si sevk edilen hastalardı. Yatan hastaların ortalama gestasyonel yaşı (GY) ve doğum ağırlığı (DA) sevk edilen hastalara göre anlamlı olarak düşüktü (p=0,09 ve p=0,024, sırasıyla). Zon 1 ROP'u saptanan yatan hastaların ortalama GY ve DA sevk edilen hastalara göre anlamlı olarak düşüktü (p=0,014 ve p=0,048, sırasıyla). Yatan hastalar ve sevk edilen hastalar arasında tedavi anındaki postmenstrüel yaş veya kronolojik yaş açısından anlamlı fark yoktu (p>0,05). Hiçbir hastada retina dekolmanı gözlenmedi.*

Sonuç: *Zamanında uygulanan tedavi yöntemleri şiddetli ROP'un gerilemesinde etkilidir. Sevk edilen hastaların DA ve GY'nın yatan hastalara göre daha yüksek olması yenidoğan yoğunbakım ünitelerinin tedavi sonuçlarının farklı olabileceğini düşündürmektedir.*

Anahtar kelimeler: *prematüre retinopatisi, diod laser fotokoagülasyon, intravitreal bevacizumab enjeksiyonu, gelişmekte olan ülke*

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Yazışma adresi: Uzm. Dr. Hatice Bilge Araz Erşan, Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği, Şişli / İstanbul
e-posta: hbilgearaz@gmail.com

INTRODUCTION

In Turkey, increases in the incidence of premature births and survival rates of premature infants have resulted in a larger number of infants at risk for long-term problems associated with prematurity, including retinopathy of prematurity (ROP) and related visual loss. In a meta-analysis of Turkish literature, it was estimated that in our country, at least 1,700 preterm infants per year are at risk for developing severe ROP [1].

The percentage of the population at risk for developing severe ROP varies greatly among countries, depending on the survival rate of premature infants and the level of perinatal and neonatal care conditions. In middle-income countries such as Turkey, where neonatal care is developing and expanding, the infants affected by ROP have a far wider range of birth weights (BWs) and gestational ages (GAs) than in developed countries [2,3].

The population at risk of developing ROP is not yet well defined in Turkey. The aim of this study is to evaluate and compare the demographic and clinical characteristics of type 1 ROP inpatient infants in a standardized level 3 referral center and infants with type 1 ROP referred from other NICUs in the most developed region of our country. This will allow us to better understand the current status in this area of Turkey.

MATERIALS and METHODS

Study population and design

This study was performed in the Ophthalmology and Neonatology Departments of the Kanuni Sultan Suleyman Education and Research Hospital. The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee of the Kanuni Sultan Suleyman Education and Research Hospital. Oral and written informed consent was obtained from the legal guardians of each patient.

The medical records of the 102 preterm infants who were treated with laser photocoagulation and/or intravitreal bevacizumab injection (IVB) for type 1 retinopathy of prematurity (ROP) between June 2012 and March 2014 were reviewed. Eighty-nine patients who survived and had continued follow-up for at least 6 months were included in the study. The cases were divided into two groups: 1) inpatient infants, who were firstly treated at the institutional NICU (n=17) and 2) referred infants, who were referred from other NICUs for examination and treatment (n=72). The following demographic variables of the two groups including BW, GA, postmenstrual age and chronological age at the time of treatment were compared.

Examination and treatment protocol

The findings were classified according to the International Classification of ROP (ICROP) [4]. The need for treatment was based on the clinical algorithm developed by the Early Treatment for Retinopathy of Prematurity (ETROP) trial [5]. Of the 72 referred patients, 14 patients were treated in the NICU from which they were referred. The patients with zone 2 ROP were routinely treated with laser photocoagulation. IVB was preferred as the initial treatment for inpatient infants with zone1 and zone 2 posterior disease. However, diode laser photocoagulation was performed on any patient who were treated in another NICU or was unlikely to return for the weekly follow-up examinations. For patients treated with IVB, reactivation was determined based on the recurrence of an concomitant disease, and additional treatment was performed only if stage 3 ROP developed. For patients who experienced reactivation after IVB injection, if the disease was still in zone 1, a second macular-sparing IVB and if the disease reactivated in zone 2, diode laser photocoagulation were performed.

Statistical analysis

All of the statistical tests were performed using SPSS software version 17.0 (SPSS Inc. Chicago, IL, USA). The descriptive statistics were given as the mean±SD and the percentage. The Kolmogorov-Smirnov test was used to analyse the normal distribution of data. The Mann-Whitney U test was used for comparisons between the groups. A Pvalue of less than 0.05 was considered significant.

RESULTS

A total of 89 infants (47 female, and 42 male) were included in the study, 47 patients were female, and 42 patients were male. Table 1 shows the demographic features of the study group.

The mean GA and BW of the inpatient infants were significantly lower than those of the referred infants (p=0.009 and p=0.024, respectively); however, there were no significant differences with regards to postmenstrual or chronological age at treatment (p=0.386 and p=0.143; respectively). The mean GA and BW of the inpatient infants with zone 1 disease were significantly lower than those of the referred patients with zone 1 disease (p=0.018 and p=0.026, respectively). No significant difference in the postmenstrual or chronological age at treatment were found between these two groups of patients (p=0.103 and p=0.426; respectively). When the mean GA, BW and postmenstrual age at treatment of inpatient and referred patients with zone 2 posterior or zone 2 disease were compared, no significant differences were found (p>0.05).

When the predetermined cut-off values of GA (≤32 weeks) and BW (≤1.500 g) were applied to study infants included in the study, 8 infants had a BW of > 1500 g, and 2 of these 8 infants had a GA of > 32 weeks. The GAs of these 2 infants were 33 and 36 weeks, and the BWs were 1540 g and 2090 g, respectively. Both of these two babies were referred for treatment, and their medical records stated that they were under prenatal follow-up; thus, early ultrasonography confirmed their GAs. One of these infants was exposed to in utero asphyxia and had multiple risk factors for ROP including male gender, multiple gestation, apnea, prolonged mechanical ventilation, intrauterine growth retardation, and septicaemia.

Seventy-two of 89 infants (139 eyes) were treated with diode laser photocoagulation. Six patients (11 eyes) received additional laser photocoagulation. Twelve patients (23 eyes) were treated with additional IVB. Seventeen patients (34 eyes) received an initial IVB treatment. Thirteen infants (26 eyes) showed regression with only one injection, and 5 patients (10 eyes) showed reactivation. Two patients (4 eyes) showed reactivation in zone 1 and received a second IVB. These reactivations were followed by a third reactivation in zone 2, which was treated with laser photocoagulation. Three reactivations (6 eyes) in zone 2 were managed with laser photocoagulation. A total of 17 infants (33 eyes) were treated with a combination of IVB and diode laser photocoagulation. Eighty-five infants (167 eyes) regressed without any complication, and 4 patients (6 eyes) regressed with fundus findings such as dragging of papilla or macula and fibrotic band formation. Retinal detachment was not observed in any of the patients. The ICROP category and the treatment performed for the management of eyes with type 1 ROP are listed in Tables 2 and 3, respectively.

Table 1. The demographic characteristics of the study population.

	N	Mean gestational age (weeks)	Mean birth weight (grams)	Mean postconceptional age at treatment (weeks)	Mean postnatal age at treatment (weeks)
All infants	89	27.8±2.6 (23-36)	1098.3±317.2 (550-2090)	37.2±2.8 (32-46)	9.5±2.9 (4-20)
Zone 1 ROP	26	27±2.4 (23-31)	997.1±276.7 (600-1430)	35.4±2.1 (32-41)	8.4±2.5 (4-15)
Zone 2 posterior ROP	16	26.9±2.4 (24-32)	1028.2±283 (660-1540)	36.3±2.7 (33-44)	9.4±2.3 (5-13)
Zone 2 ROP	47	28.5± 2.6 (24-36)	1178.2±332.8 (550-2090)	38.6±2.6 (34-46)	10.1±3.2 (5-20)
Inborn infants	17	26.3±2.3 (23-32)	942.7±336.9 (590-1670)	36.7±2.6 (32-42)	10.4±3 (6-16)
Zone 1 ROP	6	25±1.7 (23-28)	781.7±319.8 (600-1430)	34.2±1.5 (32-36)	9.2±1.3 (7-11)
Zone 2 posterior ROP	4	26.7±2.1 (25-29)	1051.5±258.5 (760-1346)	37.2±2.2 (35-40)	10.5±3.1 (6-13)
Zone 2 ROP	7	27.1±2.7 (24-32)	1018.6±378.9 (590-1670)	38.6±1.9 (36-42)	11.4±3.8 (7-16)
Referred infants	72	28.1±2.5 (24-36)	1135.1±303.3 (550-2090)	37.4±2.9 (33-46)	9.3±2.9 (4-20)
Zone 1 ROP	20	27.6±2.3 (24-31)	1061.7±234 (695-1380)	35.7±2.1 (33-41)	8.2±2.8 (4-15)
Zone 2 posterior ROP	12	27±2.6 (24-32)	1020.4±301.2 (660-1540)	36±2.8 (33-44)	9±2 (5-12)
Zone 2 ROP	40	28.7±2.5 (24-36)	1206.1±321.3 (550-2090)	38.6±2.7 (34-46)	9.8±3.1 (5-20)

Values are mean±SD and range, ROP, retinopathy of prematurity, N, number of patients.

DISCUSSION

TThe aim of an effective ROP screening program is to identify infants who need treatment. In developed countries, which have evidence-based ROP screening criteria, it is easier to predict which infants are at risk for developing severe ROP. Thus, ROP is now mainly a disease of extremely preterm babies in these countries. In epidemiologic studies from Canada, the USA and the UK, the median BWs of babies needing treatment for threshold disease were reported to be 759 g (range 440-1785 g), 763 g (range 415-1255 g) and 737 g (range 450-1260 g), and the GAs were reported to be 25.6 (range 22-32); 25.4 (range 23-29) and 25.3 weeks, (range 23-32), respectively [3]. In contrast, increasing data have revealed that in developing countries, even late preterm babies are at risk for developing severe ROP, and the screening criteria in these countries should be broadened. The median BWs and GAs of babies requiring treatment are 1254.5 g (range 710-2000 g) and 29.6 weeks (range 26-36) in India [6], 1256 g (range 903-1527 g) and 28.8 weeks (range 26.3-33.5) in Iran [7], and 1331 g (range 750-2550 g) and 29.3 weeks (range 24-35) in China [8]. In Brazil, the median BW of treated infants is 900 g (range 385-1905), and the median GA is 29 weeks (23-35) [9]. However, studies of individual NICUs with good neonatal care levels in developing countries have reported narrower ranges of BWs and GAs, indicating that the screening criteria adopted from developed countries appear appropriate for their developing countries [10,11]. In accordance with these reports, if we consider only the infants from the institutional NICU, the mean BW was 942.7 g (590-1670 g), the mean GA 26.3 weeks (23-32), and all of the patients met the screening criteria. However, if all 89 infants were included, the median GA would be 27.8 (23-36) weeks, the median BW 1097 g (550-2090), and two infants do not meet the screening criteria. The determination of threshold ROP for late preterm infants and the implied need to broaden the screening criteria have been previously reported in Turkey (12-14). Furthermore, uncertainty about the population at risk of developing ROP, the development of sight-threatening ROP in late preterm infants and related medicolegal problems led some of the Turkish NICUs to broaden their ROPscreening criteria to include all infants admitted into NICUs.

Table 2. The International Classification of Retinopathy Of Prematurity (ICROP) category of the eyes with type 1 ROP.

Zone	Stage	Plus	Number of patients/eyes
I	2	+	9/18
I	3	+	17/34
II post.	2	+	8a/14a
II post.	3	+	10[a]/18[a]
II	2	+	16[b]/27[b]
II	3	+	36[b]/67[b]

[a]2 asymmetric cases with one eye stage 2, one eye stage 3 ROP
[b]5 asymmetric cases with one eye stage 2, one eye stage 3 ROP

In the 2005 revision of the ICROP (4), aggressive posterior ROP, was defined as a new disease observed in the smallest and sickest premature babies and localized in zone 1 or posterior zone 2. Because of the aggressive nature of the disease, another randomized controlled trial, the BEAT-ROP study [15], was conducted to estimate the efficacy of IVB in the management of these cases. In this study, the infants with zone 1 ROP in the IVB group had a median BW of 615.2 g, whereas those in the laser group had a median BW of 657.9 g. The GAs were 24.2 and 24.3 weeks, respectively. In the zone 2 posterior ROP infants, the median BW for those receiving IVB was 689.2 g, whereas the median BW was 680.7 g for those who received conventional laser treatment. The median GAs were 24.5 weeks and 24.5 weeks, respectively. The BWs of babies with aggressive posterior ROP reported in the BEAT-ROP study were smaller than the mean BWs of infants with zone 1 or zone 2 posterior disease observed in our study. Similar to our findings, other Turkish studies have reported the unexpected development of severe retinopathy in zone 1 in mature infants with a BW >1250 grams and GA >30 weeks [16,17]. Thus, in contrast with developed countries, in Turkey, aggressive posterior ROP is not limited to the "tiniest" babies.

In our cohort of 89 infants, none of the treated eyes progressed to retinal detachment, a finding that is likely the result of treatment at prethreshold levels and the use of IVB therapy in severe and progressive cases. The average postmenstrual age at treatment was 37.3 weeks, and the average chronological age was 9.6 weeks. The average postmenstrual age at treatment for inpatient infants (36.7 weeks) was slightly less than that of the referred patients (37.4 weeks). In contrast, the average chronological age of the inpatient infants (10.4 weeks) was slightly greater

Table 3. The treatment performed for the management of type 1 retinopathy of prematurity.

	N (%)	Laser treatment (N of patients/eyes)	Bevacizumab monotherapy (N of patients/eyes)	Combination treatment (N of patients/eyes)
Zone 1	26 (29.2)	9/18	9/18	8/16
Zone 2 posterior	16 (18)	9/18	3/6	4/8
Zone 2	47 (52.8)	43[a]/80 eyes	0	5[a]/9

[a]*1 patient received intravitreal bevacizumab injection into 1 eye.*
N, number of patients

than that of the referred infants (9.3 weeks). Much of our knowledge about the natural history of ROP was obtained from the follow-up studies of the infants enrolled in the Cryotherapy for ROP (CRYO-ROP) [18] and ETROP [5] trials. In the ETROP [5] trial, the average postmenstrual age at treatment for prethreshold ROP was 35.2 weeks, and the average chronological age was 10 weeks. In the CRYO-ROP trial, the median postmenstrual age for the development of prethreshold ROP was 36.1 weeks, and the median chronological age was 9.6 weeks. The average postmenstrual age at development of threshold retinopathy was slightly younger and the chronological age at treatment was slightly older in the ETROP study than in the CRYO-ROP study (postmenstrual age: 37 vs. 37.7 weeks; chronological age: 11.9 vs. 11.33 weeks). The median BW and GA of infants developing threshold ROP in the ETROP study [5] were less than those reported in the CRYO-ROP study [19] (BW: 740 vs. 831 g; GA: 25.6 vs. 26.5 weeks), and similarly, in our study, the mean BW and GA of the inpatient infants were less than those of the referred infants. We believe that the timing for the development of prethreshold ROP in our study was later than that observed in the ETROP and CRYO-ROP studies due to the relative maturity of infants included in our study. However, there are contradictory data from other developing countries demonstrating a similar mean postmenstrual age at treatment for threshold ROP [20] or an earlier mean postmenstrual age for onset of type 1 ROP [21] as that found in developed countries.

A timely initiation of ROP screening is crucial to enable the identification and treatment of aggressive posterior ROP, which progresses rapidly to retinal detachment without treatment [22]. The earliest treatment performed in this study was at chronological age of 4 weeks for zone 1 ROP, and a total of 12 patients were treated between 4-6 weeks for type 1 ROP. In one patient who presented for the first screening examination, stage 5 ROP was diagnosed at a chronological age of 7 weeks. Given the wide range of distribution of GA and BW for patients with zone 1 ROP and the disease's rapid progression, neonatologists should give special attention to the timing of the ROP at their initial examination. To avoid late presentation of ROP and the loss of the window of opportunity to treat, the importance of timely ophthalmological screening should be clearly explained to the families who may be already confused by the systemic problems of a preterm child. In this sense, communication with the family is a very important part of the care of a preterm infant with ROP.

The data regarding the mortality and morbidity of preterm babies in Turkey is scarce. Starting in 2002, to determine the viability limits of preterm infants and to monitor the neonatal care levels in our country, mortality rates at selected NICUs were collected. Although, the number of centers and infants increased from between the years 2002 and 2013, the mortality rate of infants with a high risk of developing ROP (<1500 g and <32 weeks) did not change significantly. In 2002, the mortality rates of infants <1500 g and <32 weeks were 23.7% and 21.9%, respectively. In 2013, the mortality rates of infants <1500 g and <32 weeks were 23% and 18.9%, respectively [23]. The NICU in our hospital is one of the major level 3 NICUs in Turkey, with more than 2800 admissions per year. In 2013, the mortality rates of infants <1500 g and <32 weeks were 20.3% and 21.2%, respectively [23]. On the other hand, the rates of severe ROP in infants <1500 g and <32 weeks were 2.4% in 2000 [24], and 3.1% in 2013. There is an insufficient number of neonatologists and trained staff to keep up with the rapidly increasing number of neonatal intensive care units (NICUs), resulting in low staff-patient ratios. The low staff-patient ratios combined with a lack of advanced technology ventilators and standardized

treatment protocols affect neonatal outcomes and have led to variations in the incidence of ROP among Turkish NICUs [1,25].

In conclusion, the timely application of current treatment methods can provide satisfactory resolution of severe ROP. The significant difference in GAs and BWs of referred and inpatient infants in our study implies that the patient outcomes at level 3 referral centers may not be representative of other private and governmental NICUs. Given that uncontrolled oxygen therapy is the main cause of severe retinopathy in more mature babies, the results of this study may reflect the variation in the application of the treatment protocols including oxygen therapy among Turkish NICUs.

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