The role of serial measurements of serum insulin-like growth factor 1 levels in the development of retinopathy of prematurity

Bayram Ali Dorum¹, Cansu Canbolat Yılmaz², Nilgün Köksal¹, Hilal Özkan¹, Meral Yıldız³, Ahmet Tuncer Özmen³

¹Department of Pediatrics, Division of Neonatology, Uludağ University School of Medicine, Bursa, Turkey

²Department of Pediatrics, Uludağ University School of Medicine, Bursa, Turkey

³Department of Ophthalmology, Uludağ University School of Medicine, Bursa, Turkey

Abstract

Aim: To determine the role of serum insulin-like growth factor-1 levels in the development of retinopathy of prematurity, which is a major cause of childhood blindness worldwide.

Material and Methods: We prospectively studied newborn infants born at a postmenstrual age of <32 weeks and birth weights <1 500 gr, between January 1st, 2015, and December 31st, 2015. A total of 40 infants were enrolled in the study. The retinal examination time was determined in accordance with the American Academy of Pediatrics recommendations for retinopathy of prematurity screening and follow-up. Retinopathy of prematurity was classified according to the international classification of retinopathy of prematurity. Serum Insulin like growth factor 1 levels were measured serially in blood samples on the 1st, 3rd, 7th, 21st, and 28th day.

Results: Among the 40 infants, 11 (27.5%) constituted the retinopathy of prematurity group and 29 comprised the non-retinopathy of prematurity group. In the retinopathy of prematurity group, the mean gestational age and birth weight was significantly lower. The demographic features of the study cohort were similar. The duration of mechanical ventilation was significantly greater in the retinopathy of prematurity group compared with the non-retinopathy of prematurity group ($p=0.036$). In terms of neonatal morbidities such as respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis, no differences were detected between the groups. The mean serum insulin-like growth factor-1 levels in retinopathy of prematurity group were significantly lower than those in the non-retinopathy of prematurity group at each time point (1st, 3rd, 7th, 21st, and 28th day of postnatal life) ($p=0.001$).

Conclusions: This study demonstrated the low serum insulin-like growth factor-1 levels was associated with retinopathy of prematurity development. (Turk Pediatri Ars 2017; 52: 10-4)

Keywords: Insulin-like growth factor 1, prematurity, retinopathy of prematurity

Introduction

As a result of technological and scientific advancements in neonatal care, the survival rates of very low and extremely low-birth-weight preterm babies have increased. However, increased survival in these babies has also increased the frequency of severe problems, mainly including bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP).

Retinopathy of prematurity is a condition observed in preterm babies that is characterized by pathologic development in the developing vascular structure of the retina. It may result in severe visual disturbance or

blindness. In developed and developing countries, it is the most important cause of blindness in childhood (1). The main risk factors related with the development of ROP include low birth weight, low gestational age, and oxygen treatment (2).

The pathogenesis of retinopathy of prematurity is not known clearly. The retinal vessels start to develop in the fourth month of gestation and a peripheral avascular area is present in preterm babies in relation with the gestational age (3, 4). In utero normal vascular growth stops (phase 1 ROP) with delivery and this avascularized retinal area becomes metabolically active and hypoxic with maturation of the baby (5).

Address for Correspondence: Bayram Ali Dorum E-mail: bayramalidorum@gmail.com

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The second phase of retinopathy of prematurity is the retinal revascularization phase induced by hypoxia and appears in the 32nd-34th weeks. This phase is similar to the other proliferative retinopathies (3). Vascular endothelial growth factor (VEGF) is a cytokine induced by hypoxia and vascular endothelial cell mitogen (3, 6). Presence of VEGF is required for normal vascular development (2, 4). High oxygen support inhibits production of VEGF in animal models and affects vascular growth in the first phase of ROP (7).

Insulin-like growth factor-1 (IGF-1), which is one of the important regulators of fetal growth, has a significant role in retinal vascularization by way of affecting vascularization directly and controlling activation of VEGF (8). Insulin-like growth factor-1 acts synergistically with VEGF in increasing angiogenesis. High IGF-1 levels are required in retinal endothelial cells for the highest VEGF activation, and these are also required for endothelial cell proliferation (9). In IGF-1 deficiency in the postnatal early stage in mouse experiments, the key role of IGF-1 in normal retinal development was demonstrated by showing that vascularization was delayed markedly, even if VEGF levels were normal (8).

In this study, we aimed to investigate the relation between IGF-1 levels measured on different days and ROP in preterm babies carrying a risk of ROP.

Material and Methods

Ethics committee approval was obtained from Uludağ University Ethics Committee for the study (2014-2/24 - 01.28.2014). Preterm babies with a gestational age of ≤ 32 weeks and a birth weight of ≤ 1500 g who were hospitalized in the Neonatal Intensive Care unit of our university between January 1st, 2015, and December 31st, 2015, were included in this prospective study. Babies with major morphologic anomalies were excluded from the study. Oxygen treatment was administered, when necessary, in all babies during the hospitalization period such that the target oxygen saturation was kept between 90% and 95%. Total parenteral nutrition (TPN) was given to the babies until the enteral nutrition reached 100 mL/kg/day. For measurement of IGF-1, venous blood samples were obtained on the 1st, 3rd, 7th, 21st, and 28th days together with blood samples obtained for routine hematologic and biochemical tests. The blood samples were immediately centrifuged at 3000 rpm for five minutes. The serum part was transferred into Eppendorf tubes and kept at -20°C. Measurements in all

samples were performed in accordance with the protocol recommended by the manufacturing company using commercial quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (SUNRED, Shanghai).

Retina examinations were performed with consideration to the American Academy of Pediatrics ROP screening and follow-up criteria (10). The examinations were performed by the same pediatric ophthalmologist who was blinded to the study using an indirect ophthalmoscope. The pupils were dilated weekly or every two weeks from the postnatal fourth week in the babies with a gestational age of 27 weeks and above and from the postmenstrual 31st week in babies with a gestational age of <27 weeks. Staging of retinopathy of prematurity was made according to the international ROP classification (11). The diagnosis and classification of bronchopulmonary dysplasia was made according to the new BPD criteria (12). The babies were evaluated using cranial ultrasonography in terms of intraventricular hemorrhage (IVH) and grouped according to the Papile classification (13). The diagnosis and classification of necrotizing enterocolitis (NEC) was made according to the modified Bell criteria (14).

Statistical analysis

Written informed consent was obtained from the families. Statistical analyses were performed using the Statistical Package for the Social Sciences version 22.0 (Armonk, NY, IBM Corp., USA). Correlations between the variables and statistical differences were examined using the Mann-Whitney test. A p value of <0.05 was considered statistically significant.

Results

The mean gestational age of 40 babies included in the study was found as 29.41 ± 2.23 weeks and the mean birth weight was 1256 ± 311 g. Twenty-one (52.5%) of the babies were female and 19 (47.5%) were male. ROP was found in a total of 11 babies (27.5%), nine of whom had grade 1 ROP (22.5%), one had grade 2 ROP (2.5%), and one had grade 3 ROP (2.5%). Grade 4 ROP and grade 5 ROP or ROP requiring treatment were not found in any patients. When the patients with and without ROP were compared in terms of maternal and neonatal characteristics, no significant difference was found between the groups (Table 1).

Twenty-five (62.5%) babies were diagnosed as having respiratory distress syndrome (RDS). NEC developed in

Table 1. Demographic properties of the patients

	ROP + (n=11)	ROP - (n=29)	^a p
Maternal properties			
Cesarean section, n (%)	9 (81.8)	26 (89.7)	>0.05
Preeclampsia, n (%)	3 (27.3)	9 (31)	>0.05
Chorioamnionitis, n (%)	2 (18.2)	1 (3.4)	>0.05
Premature rupture of the membranes, n (%)	3 (27.3)	6 (20.7)	>0.05
Antenatal steroid, n (%)	8 (72)	27 (93)	>0.05
Neonatal properties			
Gestational age (day), mean±SD	28.27±2.2	29.48±2.2	>0.05
Birth weight (g), mean±SD	1178±34	1286±30	>0.05
Male sex, n (%)	4 (36.4)	15 (51.7)	>0.05
Apgar score ^{1.min} , mean±SD	4.3±0.9	4.6±2.2	>0.05
Apgar score ^{5.min} , mean±SD	5.0±2.5	6.8±2.7	>0.05

^aMann-Whitney U test

ROP: retinopathy of prematurity

Table 2. Comparison of the other problems of the patients

	ROP + (n=11)	ROP - (n=29)	^a p
Total days of O ₂ , mean (min-max)	56.36 (14-208)	32 (2-178)	>0.05
Mechanical ventilator days, mean (min-max)	30.90 (1-115)	11.27 (0-92)	0.036
Noninvasive ventilation days, mean (min-max)	20.81 (1-93)	12.75 (1-70)	>0.05
Respiratory distress syndrome, n (%)	8 (72)	17 (58)	>0.05
Bronchopulmonary dysplasia, n (%)	6 (54.5)	8 (27.6)	>0.05
Necrotizing enterocolitis, n (%)	2 (18)	4 (13)	>0.05
Patent ductus arteriosus, n (%)	3 (27)	11 (37)	>0.05
Intraventricular hemorrhage, n (%)	5 (45)	10 (34)	>0.05

^aMann-Whitney U test

ROP: retinopathy of prematurity

Table 3. Comparison of Serum IGF-1 levels by the state of retinopathy of prematurity

IGF-1 (ng/mL) level	ROP		^a p
	Present (n=11)	Absent (n=29)	
1 st day mean±SD	10.61±0.91	24.85±10.37	0.001 ^b
3 rd day mean±SD	8.44±2.46	25.72±10.91	0.001 ^b
7 th day mean±SD	10.63±2.56	26.44±10.06	0.001 ^b
21 st day mean±SD	11.42±1.3	24.04±9.85	0.001 ^b
28 th day mean±sd	12.83±3.3	29.33±12.86	0.001 ^b

^aMann-Whitney U test, ^bp<0,01

IGF-1: insulin-like growth factor-1; Rop: retinopathy of prematurity

six patients (15%), IVH developed in 15 patients (37.5%), and BPD developed in 14 patients (35%). Treatment was administered in 14 patients (35%) because of hemodynamically significant BPD. No difference was found between the patients with and without retinopathy of prematurity in terms of these problems. However, the time periods of requirement for mechanical ventilation were found statistically significantly longer in patients who developed ROP (Table 2, p<0.05).

When compared in terms of serum IGF-1 levels, it was observed that serum IGF-1 levels on the 1st, 3rd, 7th, 21st, and 28th days were significantly lower in patients who developed ROP compared with those who did not develop ROP (Table 3, p<0.05).

Discussion

Retinopathy of prematurity is a significant problem observed in preterm babies and the most common cause of childhood blindness. In a study conducted in our country, in which 15,745 preterm babies were examined, the frequency of ROP was found as 30% and the frequency of treatment requiring ROP was 5%. These rates were found as 35.6% and 6.5% in babies with a gestational age of 32 weeks and below (15). In the present study, in which we examined preterm babies with a gestational age of 32 weeks and below, the frequency of ROP was 27.5% and treatment-requiring ROP was not found in any patients.

Preterm babies who have been discharged from neonatal intensive care units should be protected against ROP and screened and treated in time and appropriately in order to increase their quality of life. Exposure to oxygen, extremely low birth weight and low gestational week are the main known risk factors for ROP. Various studies investigated indicators that could be used to determine development of ROP in the early stage. In the study conducted by Çetinkaya et al. (16), it was shown that plasma sE-selectin levels were significantly lower in the early stage in preterm babies who developed ROP compared with those who did not develop ROP.

In a study conducted by Husain et al. (17), weight gain as well as birth weight and gestational age was found significantly lower in the early stage in patients who had treatment-requiring ROP. They also showed that being of black race was protective against ROP (16).

Lundgren et al. (18) followed up the gestational age and weekly weight gain in babies below the 32nd gestational week using WINROP (weight, insulin-like growth factor 1, neonatal, retinopathy of prematurity) analysis, which they developed in Sweden and succeeded to determine severe ROP cases with a sensitivity of 95.7%.

Binenbaum et al. (19) determined all cases of severe ROP using the CHOP ROP model, which they developed using birth weight, gestational week, and daily weight gain, and reduced the frequency of recurrent follow-up visits by 49% by monitoring the babies according to the risk states found in this model.

The relationship of weight gain with the development of ROP has been explained in different ways. Weight gain after delivery in preterm babies is affected by many factors including disease severity, feeding intolerance, frequency of septic events, and prolonged mechanical respiratory support. Insufficient intake of protein and energy under these conditions inhibits normal retinal vascularization (17). In addition, babies with malnourishment have low serum IGF-1 levels and this increases the risk in terms of the development of ROP by disrupting VEGF signalization (8).

In a study conducted by Hellstrom et al. (8), weekly IGF-1 levels were examined and reduced IGF-1 level was shown as related with development of ROP. Perez et al. (20) showed that low IGF-1 levels were a risk factor in terms of the development of ROP independent of gestational week and increased IGF-1 levels were related with regression of ROP.

In accordance with the literature, the mean serum IGF-1 levels measured on the 1st, 3rd, 7th, 21st, and 28th days were statistically significantly lower in babies who developed ROP compared with those who did not develop ROP in the present study. In contrast to fetal life, a marked increase was not observed in IGF-1 levels during the four-week follow-up period. This result suggests that low IGF-1 levels have a significant role in the development of ROP. It is thought that administration of IGF-1 in this phase will prevent progression to the second phase because the effects related with deficiency of growth factors are observed especially in the first phase of ROP development (3).

In conclusion, this study showed that reduced serum IGF-1 levels might be a factor related with the development of ROP. Although the number of our subjects was

low, preterm babies with low serum IGF-1 levels seem to have an increased risk in terms of ROP development. We think that more comprehensive studies should be performed to fully elucidate the role of IGF-1 in the pathogenesis of ROP and to investigate the effects of IGF-1 support in terms of the prevention of ROP.

Ethics Committee Approval: Ethics committee approval was received for this study from Uludağ University Ethics Committee.

Informed Consent: Written informed consent was obtained from patients' parents, who participated in this study.

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References

- Li ML, Hsu SM, Chang YS, et al. Retinopathy of prematurity in southern Taiwan: a 10-year tertiary medical center study. *J Formos Med Assoc* 2013; 112: 445-53. [\[CrossRef\]](#)
- Cavallaro G, Filippi L, Bagnoli P, et al. The pathophysiology of retinopathy of prematurity: An update of previous and recent knowledge. *Acta Ophthalmol* 2014; 92: 2-20. [\[CrossRef\]](#)
- Smith LEH. IGF-1 and retinopathy of prematurity in the preterm infant. *Biol Neonate* 2005; 88: 237-44. [\[CrossRef\]](#)
- Chen J, Smith LEH. Retinopathy of prematurity. *Angiogenesis* 2007; 10: 133-40. [\[CrossRef\]](#)
- Sen P, Rao C, Bansal N, Mahavir SB. Retinopathy of prematurity : An update on screening and management. *Pediatric Child Health* 2016; 21: 101-4.
- Stahl A, Hellstrom A, Smith LEH. Insulin-like growth factor-1 and anti-vascular endothelial growth factor in retinopathy of prematurity: Has the time come? *Neonatology* 2014; 106: 254-60. [\[CrossRef\]](#)
- Çetinkaya M, Köksal N, Özkan H. Prematüre retinopati-si ile serum insülin benzeri büyüme faktörü-1 düzeyleri arasındaki ilişki. *Güncel Pediatri* 2008; 2: 47-52.
- Hellstrom A, Engstrom E, Hard A-L, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* 2003; 112: 1016-20. [\[CrossRef\]](#)
- Reddy MA, Patel HI, Karim SM, et al. Reduced utility of serum IGF-1 levels in predicting retinopathy of prema-

- turity reflects maternal ethnicity. *Br J Ophthalmol* 2016; 100: 501-4. [\[CrossRef\]](#)
10. Academy A, Ophthalmology P. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2013; 131: 189-95. [\[CrossRef\]](#)
 11. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. *Arch Ophthalmol* 2005; 123: 991-9. [\[CrossRef\]](#)
 12. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723-9. [\[CrossRef\]](#)
 13. Burstein J, Papile LA, Burstein R. Intraventricular hemorrhage and hydrocephalus in premature newborns: A prospective study with CT. *Am J Roentgenol* 1979; 132: 631-5. [\[CrossRef\]](#)
 14. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: Therapeutic decisions based upon clinical staging. *Ann Surg* 1978; 187: 1-7. [\[CrossRef\]](#)
 15. Bas AY, Koc E, Dilmen U. Incidence and severity of retinopathy of prematurity in extremely premature infants. *Can J Ophthalmol* 2012; 47: 296-300. [\[CrossRef\]](#)
 16. Çetinkaya M, Erener-Ercan T, Cansev M, et al. The utility of serial plasma sE-selectin measurements in the prediction of retinopathy of prematurity in premature infants. *Early Hum Dev* 2014; 90: 517-21. [\[CrossRef\]](#)
 17. Husain SM, Sinha AK, Bunce C, et al. Relationships between maternal ethnicity, gestational age, birth weight, weight gain, and severe retinopathy of prematurity. *J Pediatr* 2013; 163: 67-72. [\[CrossRef\]](#)
 18. Lundgren P, Stoltz Sjöström E, Domellöf M, et al. WINROP identifies severe retinopathy of prematurity at an early stage in a nation-based cohort of extremely preterm infants. *PLOS One* 2013; 8: 1-6. [\[CrossRef\]](#)
 19. Binenbaum G, Ying G-S, Quinn GE, et al. The CHOP postnatal weight gain, birth weight, and gestational age retinopathy of prematurity risk model. *Arch Ophthalmol* 2012; 130: 1560-5. [\[CrossRef\]](#)
 20. Pérez-Muñuzuri A, Fernández-Lorenzo J, Couce-Pico M, Blanco-Teijeiro M, Fraga-Bermúdez J. Serum levels of IGF1 are a useful predictor of retinopathy of prematurity. *Acta Paediatr Int J Paediatr* 2010; 99: 519-25. [\[CrossRef\]](#)