• Clinical Research •

A predictive score for retinopathy of prematurity by using clinical risk factors and serum insulin-like growth factor-1 levels

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Abstract

• AIM: To detect the impact of insulin-like growth factor-1 (IGF-1) and other risk factors for the early prediction of retinopathy of prematurity (ROP) and to establish a scoring system for ROP prediction by using clinical criteria and serum IGF-1 levels.

• METHODS: The study was conducted with 127 preterm infants. IGF-1 levels in the 1st day of life, 1st, 2nd, 3rd and 4th week of life was analyzed. The score was established after logistic regression analysis, considering the impact of each variable on the occurrences of any stage ROP. A validation cohort containing 107 preterm infants was included in the study and the predictive ability of ROP score was calculated.

• RESULTS: Birth weights (BW), gestational weeks (GW) and the prevalence of breast milk consumption were lower, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) were more frequent, the duration of mechanical ventilation and oxygen supplementation was longer in patients with ROP (*P*<0.05). Initial serum IGF-1 levels tended to be lower in newborns who developed ROP. Logistic regression analysis revealed that low BW (<1250 g), presence of intraventricular hemorrhage (IVH) and formula feeding increased the risk of ROP. Afterwards, the scoring system was validated on 107 infants. The negative predictive values of a score less than 4 were 84.3%, 74.7% and 79.8% while positive predictive values were 76.3%, 65.5% and 71.6% respectively.

• CONCLUSION: In addition to BW <1250 g and IVH, formula consumption was detected as a risk factor for the development of ROP. Breastfeeding is important for prevention of ROP in preterm infants.

• KEYWORDS: retinopaty of prematurity; insulin-like growth factor-1; breast milk; protectivity

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INTRODUCTION

Retinopathy of prematurity (ROP) is a clinically multifactorial process that can cause blindness in preterm infants. The prevalence of ROP ranges from 0-30%, depending on the quality of neonatal care and the set of individual risk factors[1-2]. Several risk factors have been reported as involved in the development of ROP but birth weight (BW) and gestational age (GA) are considered the most important risk factors for disease onset[3]. Therefore many ROP screening protocols are based on BW and GA. American Academia of Pediatrics (AAP) recommends screening for babies with BW ≤1500 g and GA ≤30wk. Also the infants whose BW is 1500-2000 g but having an unstable clinical course or requiring respiratory support are recommended to undergo ocular examination for

ROP screening[4]. A recent multicenter trial conducted by the Neonatal Study Group in Turkey demonstrated that 13% of preterm infants with GA 32-34wk developed ROP and 4/1000 required treatment for ROP[5].

The main cause of ROP is the incomplete vascularization of the retina in preterms. In addition to small GA and low BW, miscellaneous risk factors including hyperoxia, hypoxia, acidosis, intraventricular hemorrhage (IVH), exposure to light, vitamin E deficiency and septicemia have been reported[6].

Insulin-like growth factor-1 (IGF-1) is an endocrine and autocrine/paracrine growth factor in the plasma which is expressed in most cells in the body. It has effects on cell growth and differentiation, development and tissue repair. Recently IGF-1 has been shown to play a role in the pathophysiology of ROP development. Especially, lower IGF-1 levels in the first week of life can lead to proliferative stages of ROP[7-8]. Pérez-Muñuzuri *et al*[7] attempted to develop a screening method for the prediction of ROP based on serum levels of IGF-1 in the 3rd week and the presence or absence of sepsis in the first 3wk.

In this study, we aimed to evaluate whether serum IGF-1 levels in the first 4wk of life in addition to clinical criteria offer a better screening protocol for ROP or not in developing countries.

SUBJECTS AND METHODS

Study Design This prospective trial was conducted in Bahcesehir University School of Medicine, Goztepe Medicalpark Hospital Neonatal Intensive Care Unit (NICU) between January 2013 and January 2015. Our unit is a level III NICU with 22 incubators and approximately 300 annual admissions.

The study protocol was approved by the Ethics Committee of the Haydarpasa Gulhane School of Military Medicine (GATA) with the protocol number 2014-86. The written informed consent from the parent was obtained for each child prior to the study. Near East University Center of Excellence was the funding source relevant to the study.

Population Preterm infants born ≤34wk of GA were enrolled. The preterm infants who were transferred to our unit after 24h of life, having congenital anomalies (cardiac, pulmonary, gastrointestinal and cranial) or metabolic diseases, the preterm infants who had TORCH infection and the ones who died before 4wk of age were excluded.

All preterm infants ≤34wk of GA followed until discharge and statistical analysis was done according to the result of ROP screening. The preterm infants who developed ROP composed the study group and the preterm infants who didn't have ROP composed the control group. After determination of the optimal clinical scoring system, it was validated prospectively on all NICU admissions who were <34wk of GA at the same hospital between November 2016 to February 2017 (validation cohort) in order to test the predictive accuracy of the scoring system.

Selection of Variables for Clinical ROP Score The selection of variables to compose the clinical score was based on the analysis of risk factors for ROP. Sixteen variables analyzed: GA, BW, gender, antenatal steroids, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), use of mechanical ventilation, use of oxygen by nasal cannula, IVH at any grade, necrotizing enterocolitis (NEC) at any grade, patent ductus arteriosus (PDA), blood transfusion requirement, nasocomial sepsis, full enteral feeding days, time to catch-up of BW, hospitalisation days and feeding type (breast milk or formula).

GA was calculated according to the mothers' last menstrual history or estimated from the Ballard score. RDS was defined as respiratory distress with characteristic radiographic findings[9]. Infants having the need of mechanical ventilation or oxygen treatment more than 28d were defined as to have BPD[10]. IVH was diagnosed by cranial ultrasound and classified according to Papile grading system[11]. NEC was diagnosed by clinical and radiological findings according to Bell's staging criteria[12]. Transthoracic echocardiography was performed for the diagnosis of PDA[13]. Sepsis or meningitis were diagnosed according to culture results. Relative weight gains (body weight minus BW, divided by BW and postnatal age) at the second and fourth weeks of life were calculated (g/kg/day). ROP screening examination was done by a senior ophthalmologist who was experienced in the diagnosis of ROP. All the ophthalmologic examinations were done at the 4-6th week postnatally according to AAP protocol[3].

Laboratory Tests and Methods Serum IGF-1 levels were analyzed by ELISA kits (DIA source Human IGF-1, Catalogue number: KAP1581, ImmunoAssays S.A., Louvain-la-Neuve, Belgium; sensitivity 7.8 ng/mL). The blood samples for serum IGF-1 levels were drawn in the first 24h of life and then weekly (1 to 4wk) in the postnatal period. Preprandial blood samples were taken by venipuncture through a venous catheter at 7 a.m. The EDTA tubes were immediately centrifuged for 10min at 1000 g. Serum was separated and frozen at -20℃ until analysis.

Statistical Analysis Statistical analysis was performed with SPSS Statistics 17.0. Numerical variables were tested for normal distribution. For analysis of continuous data, independent-samples *t*-test or Mann-Whitney *U* test was used as appropriate, to detect differences between the groups. Categorical variables were analyzed by using Pearson Chi-square test or Fisher's exact test as appropriate. The level of statistical significance was considered as $P<0.05$ (two-tailed). Binary logistic regression analysis was also performed for composing the score system. The scoring system was developed by assigning points to categories significantly associated with ROP risk, taking into account their risk ratios (RR) from the logistic regression model. Hosmer-Lemeshow

Table 1 Demoghrapic charecterictics of newborns *n* (%)

Parameters	Study group	Control group	*P*
Gestational weeks (mean±SD)	29.14±2.40	30.74±1.95	<0.001[a]
Birth weight (g) (mean±SD)	1184.63±361.30	1545.89±416.49	<0.001[a]
Gender			1.000[b]
Male	21 (48,8)	40 (65.6)	
Female	22 (51.2)	44 (66.7)	
Antenatal steroid			0.253[b]
Yes	38 (36.9)	65 (63.1)	
No	5 (21.7)	18 (78.3)	
Respiratory distress syndrome			<0.001[c]
Mild	12 (21.8)	43 (78.2)	
Moderate	11 (26.2)	31 (73.8)	
Severe	20 (66.7)	10 (33.3)	
Bronchopulmonary dysplasia			0.004[b]
Yes	28 (48.3)	30 (51.7)	
No	15 (22.1)	53 (77.9)	
Duration of mechanical ventilation (d) (mean±SD)	41.58±41.77	19.54±25.19	<0.001[a]
O_2 suplementation (d) (mean±SD)	51.22±43.98	28.15±28.35	<0.001[a]
Intraventricular hemorrhage			<0.001[b]
Yes	20 (60.6)	13 (39.4)	
No	23 (24.5)	71 (75.5)	
Necrotizing enterocolitis			0.003[b]
Yes	24 (51.1)	23 (48.9)	
No	19 (23.8)	61 (76.3)	
Any erythrocyte transfusion			0.014[b]
Yes	32 (43.2)	42 (56.8)	
No	11 (20.8)	42 (79.2)	
Full enteral feeding days (mean±SD)	24.14±14.57	18.01±20.75	0.001[a]
Catch-up day (mean±SD)	12.93±6.77	11.92±3.96	0.602[a]
Hospitalisation days (mean±SD)	57.56±42.17	38.61±44.94	<0.001[a]
Nosocomial sepsis			0.008[b]
Yes	21 (51.2)	20 (48.8)	
No	22 (25.6)	64 (74.4)	
Feeding style			0.001[b]
Breast milk	21 (24.1)	66 (75.9)	
Formula	22 (55)	18 (45)	
Relative weight gain at the 2wk (g/kg/d) (mean±SD)	3.86±1.18	3.25±0.57	0.88
Relative weight gain at the 4wk (g/kg/d) (mean±SD)	9.54±0.83	10.47±0.57	0.5

[a]Mann-Whitney *U*; [b]Chi-square test (with continuity correction); [c]Pearson Chi-square test.

goodness of fit statistics and correlation matrices of parameter estimates were investigated to assess model fit. Spearman correlation coefficients were used to assess the correlation between ROP and the score.

RESULTS

During the study period, a total number of 127 preterm infants ≤34wk of GA were assessed for eligibility. We composed 2 groups as study group (patients with ROP) and control group (patients without ROP). Forty-three infants (33.8%) had ROP and 84 infants (66.2%) didn't have ROP. Demographic characteristics of the groups are shown in Table 1. The incidence of severe ROP that require treatment in our population was 6/127 patients (4.7%). There were no patients that required vitroretinal surgery.

The mean BW and GA were lower in the study group (*P*<0.001) but there was no difference between the genders (*P*=1.000) and the use of antenatal steroids (*P*=0.253). Comparison of the study group with the control group revealed statistically significant differences in percentage of severe RDS, duration of mechanical ventilation and O_2 therapy, presence of ROP, IVH, NEC, sepsis and blood transfusion being all factors higher in the study group.

Moreover, reaching to full-enteral feeding (postnatal day), formula feeding and the duration of hospitalisation were significantly high in the study group.

On the other hand, the relative weight gain with in the 2nd and 4th weeks of life were not different between groups (P>0.05). Serum IGF-1 levels of the preterm infants in the 1st day of life, 1st, 2nd, 3rd and 4th week of life were not statistically different (P>0.05) (Table 2). The mean IGF-1 levels at birth tended to be lower in the study group but this was not statistically significant. Logistic regression analysis revealed that low BW (<1250 g), presence of IVH and formula feeding increased the risk of ROP (RR=4.7 for BW<1000 g, RR=3.3 for BW 1000-1250 g, RR=2.9 for any stage IVH, RR=2.9 for exclusive formula feeding). Logistic regression analysis results are shown in Table 3.

All variables selected to compose the score were considered statistically significant for ROP outcomes after univariate analysis and multivariate analysis (logistic regression). The score was established after linear regression according to the impact of each variable in relation to ROP onset. According to RR we predicted to give 5 points for the BW less than 1000 g and 3 points for the BW 1000-1250 g, IVH and formula feeding.

The ROP scores were further used prospectively in 107 neonates (validation cohort). Demoghraphic and clinical characteristics of validation cohort was shown in Table 4. IGF-1 levels at birth, first, second, third and forth weeks were not statistically significantly different between study and control groups (Figure 1). ROC curves for ROP score for the derivation, validation and all (entire) cohorts' datasets in predicting ROP were calculated (Figure 2). The area under the curve value of validation cohort was 0.734 (SE): 0.050, 0.821 (SE): 0.043 for derivation and 0.821 (SE): 0.043 for all cohort. Optimal cut point for score was calculated as 4. The negative predictive values of a score less than 4 were 84.3%, 74.7% and 79.8%, while positive predictive values of a score more than 4 were 76.3%, 65.5% and 71.6% respectively.

Table 2 IGF-1 levels of newborns Mean±SD; ng/mL

Time	ROP (+)	ROP (-)	P
IGF-1 at birth	22.379±6.009	24.991±8.437	0.063[a]
IGF-1 1st wk	25.388±9.426	27.755±11.317	0.362[a]
IGF-1 2nd wk	27.845±8.232	26.033±8.584	0.098[a]
IGF-1 3rd wk	26.413±8.925	28.118±9.403	0.659[a]
IGF-1 4th wk	30.491±15.695	28.917±9.309	0.073[a]

[a]Mann-Whitney U.

Table 3 Scores of ROP risk after logistic regression analysis

Parameters	Value	Relative risk	Point
BW	<1000 g	4.7 (1.35-16.25)	5
	1000-1250 g	3.3 (1.23-8.91)	3
	>1250 g	1.0	0
IVH	Negative	1.0	0
	Positive	2.9 (1.13-7.33)	3
Feeding type	Breast milk	1.0	0
	Formula milk	2.9 (1.21-7.22)	3

Table 4 Demographic and clinical charesteritics of study and validation cohorts n (%)

Parameters	Study group (n=127)	Validation group (n=107)	P
GW (wk) (mean±SD)	30.2±2.24	31.18±2.64	0.003
BW (g) (mean±SD)	1423±432	1573.93±505	<0.001[a]
Gender (male)	61 (48)	49 (45.3)	0.5
RDS			0.6
Mild	51 (40.2)	38 (35.1)	
Moderate	42 (33.1)	29 (27)	
Severe	30 (23.6)	39 (36.1)	
BPD	54 (42.5)	42 (39)	0.001
Any stage ROP	42 (33.1)	88 (81.4)	0.001
IVH	33 (26)	23 (21.2)	0.092
Breast milk	87 (68.5)	57 (52.7)	0.06

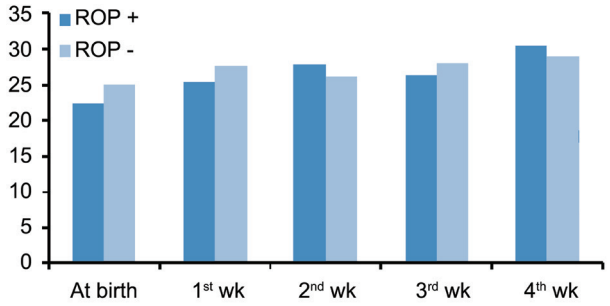

Figure 1 IGF-1 levels (ng/mL) of ROP and non-ROP groups.

DISCUSSION

In this study we demonstrated that low BW (<1250 g), formula feeding and having IVH increased the risk of ROP significantly. In addition, IGF-1 levels at birth are tended to be lower in infants who developed ROP, although which was not statistically significant. The use of predictive scores is very important in neonatology. Several scoring systems like Clinical Risk Index for Babies II (CRIB II) are routinely used as predictors of several comorbidities. CRIB II score is a validated measure of initial mortality risk and illness severity which is used within one hour of admission. BW, GA, body temperature, base excess and sex of the baby are used to determine initial mortality risk. The CRIB II score ranged from 0 to 27 and lower scores predicts better prognosis[14]. Weight, IGF-1, neonatal ROP (WINROP) study has demonstrated that weight gain and IGF-1 levels are highly predictive markers for ROP[15]. A predictive score for ROP should incorporate variables that take into account the clinical course of the patient as well as the degree of immaturity.

In this article we aimed to evaluate whether serial analysis of IGF-1 levels are helpful in predicting the risk of developing ROP in preterm infants in addition to clinical parameters.

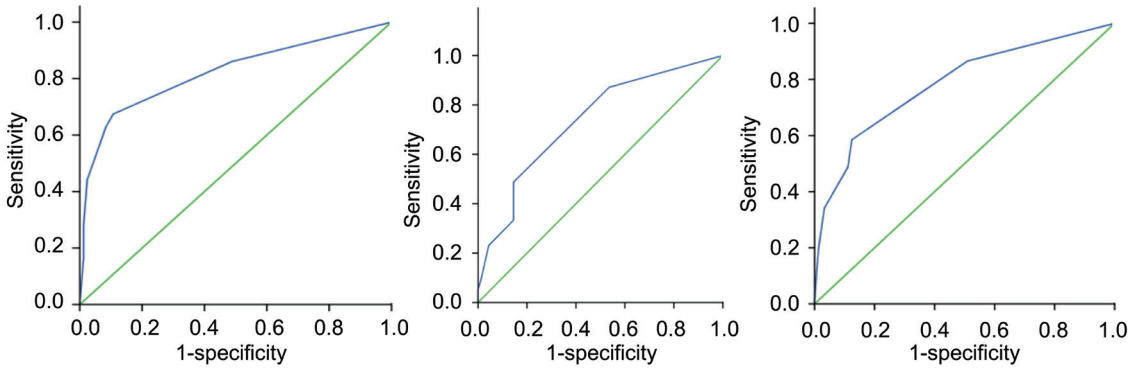

Figure 2 ROC curves for ROP score for the derivation, validation and entire cohorts datasets in predicting ROP.

Univariate comparisons revealed that low BW and GA, presence of RDS, BPD, longer duration of mechanical ventilation and oxygen therapy, IVH, NEC, PDA, blood transfusion, sepsis, and formula feeding are the risk factors for ROP. On the other hand, multivariate analysis revealed that low BW, IVH and formula feeding were the only risk factors for developing ROP. Although, relative weight gain during the first month of life was reported as a risk factor for developing ROP, no significant relation was detected in our study group[16-19].

An ideal method to predict ROP would have high positive and negative predictive values and should be applicable very early in life. The discrimination ability of a score is very important and it is measured by the area under the ROC curve (AUC). A value above 0.7 indicates that the score may be useful in practice and moreover having a value more than 0.8, shows the score is good[20]. In the ROP score, AUC values for the derivation and the validation cohorts were 0.821 and 0.734 which were compatible with that criteria. Reproducibility of the scoring system is very important. We have validated our score in the same unit. The ROP scores had similar ROC curves and predictive capacity in both populations. These results suggest that our ROP score system is useful for predicting the development of ROP.

The retina of a preterm infant at birth is incompletely vascularized and if the postnatal environment does not match the inutero environment that supported retinal development, retinal vessels will not grow normally, resulting in ROP development[3]. Previous studies characterized ROP as a two phased disease with initial cessation of vessel growth caused by exposure to high levels of oxygen and loss of formed vessels (phase I) followed by pathological neovascularization of the retina (phase II)[16].

IGF-1 is a polypeptide that promotes human fetal growth throughout gestation but particularly in the third trimester. The sudden loss of the maternal fetal interaction contributes to the dramatic reduction in serum IGF-1 after preterm birth. IGF-1 synthesis in the liver of the fetus/preterm infant is dependent on nutrient supply and level of maturity[21-23].

Animal studies have shown the importance of low IGF-1 in the development of ROP[24-25]. Growth hormon and IGF are important in angiogenesis. IGF-1 is necessary for maximum VEGF signalling pathways for endothelial cell survival and proliferation[26]. Low IGF-1 levels might promote poor vascular growth seen in phase I of ROP by effecting VEGF signaling in the preterm infants[15]. In this study, IGF-1 levels in the 1st day of life, 1st, 2nd, 3rd and 4th weeks were measured. IGF-1 levels in the first day of life were lower in the preterms that developed ROP. Although not statistically significant, this is an important finding that should be confirmed in future studies with larger samples. Recently, the Can *et al*[27] demonstrated that early aggressive parenteral nutrition (EAPN), especially protein intake increases serum IGF-1 levels of preterms. Increase in IGF-1 may have an impact on VEGF signalling pathway, for endothelial proliferation and therefore vascularisation which may be preventive for ROP.

Our study also demonstrated that, formula milk instead of breast milk is an important risk factor for the development of ROP which confirms the importance of nutrition in this respect. According to the Meta-analysis by Zhou *et al*[28], the overall incidence of ROP was reduced among infants who fed by breast milk compared to formula milk. However, some studies reported no benefits of breast milk on ROP development[28-29]. The contents of breast milk such as antioxidants (vitamin C, vitamin E, β-carotene) and immune-protective substances (secretory IgA, lactoferrin, lysozyme, cytokines, olgosaccharides, antioxidant enzymes and celluler components) of breast milk may be involved in the physiologic mechanism which rate in the protection ROP[28,30-31].

In conclusion, this study demonstrated that low BW, IVH and formula feeding instead of breast milk are important risk factors for the development of ROP. Low IGF-1 levels detected at birth may have a predictive value for the development of ROP. Further studies are warranted to confirm this issue in order to attempt to increase the IGF-1 levels since birth by nutritional support.

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