Poor postnatal weight gain predicts stage 3+ retinopathy of prematurity in very low birth weight infants

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Multiple systemic risk factors are associated with retinopathy of prematurity (ROP). We analyzed the role of low weight gain (WG) to predict the development of stage 3+ ROP among preterm infants. This study included 126 newborns with birth weight ≤1500 g and gestational age <32 weeks. Preterm newborn infants were divided into two groups according to severity of ROP as: preterm infants without ROP or mild ROP (Group 1) and preterm infants with stage 3+ ROP (Group 2). WG and WG proportion were measured at completed 4 and 6 weeks of life. The patients under the cut-off point according to receiver operating characteristic curve were classified as low WG patients. WG and WG proportion were significantly lower in Group 2 than in Group 1 at the 4th and 6th weeks of life. We concluded that low WG and WG proportion at the 4th and 6th weeks of life were predictive for the development of stage 3+ ROP. Preterm babies with low birth weight and low WG should be followed closely for severe ROP.

Key words: low weight gain, retinopathy of prematurity, weight gain proportion.

Retinopathy of prematurity (ROP) is a multifactorial disease that is characterized by abnormal vascular proliferation of the retina[1,2]. ROP is a major cause of preventable blindness in children all over the world[3-5]. Multiple systemic risk factors are associated with ROP, including low gestational age, low birth weight, oxygen exposure, mechanical ventilation therapy, respiratory distress syndrome, sepsis, intraventricular hemorrhage, and erythrocyte transfusions[6-8]. There are few studies investigating the relationship between low weight gain (WG) and ROP[9-12]. We aimed to determine the role of postnatal WG in the development of severe ROP.

Material and Methods

In this study, 126 preterm infants born with gestational age of 24-32 weeks and weighing ≤1500 g at Başkent University Hospital, Turkey, between April 2008 and October 2011 were recruited. The first ROP examination was performed at the 4th or 6th week of life. The study protocol was approved by the Ethics Committee at Başkent University Faculty of Medicine. The ophthalmic examinations were performed by the same author and consisted of indirect ophthalmoscopy and the lid speculum for newborns. The pupils were dilated with eye drops containing tropicamide 0.5% and phenylephrine 2.5%. The ROP examination was performed once or twice a week depending on the severity of the disease or until retinal vascularization was completed. ROP was classified according to the International Classification of ROP[3]. Stage 3+ ROP was accepted as the threshold for treatment and was detected between the 4th and 6th weeks of life. Preterm infants were divided into two groups according to the severity of ROP as: preterm infants without ROP or mild ROP (Group 1), and preterm infants with stage 3+ ROP (Group 2). WG at four weeks (WG from birth - week 4) and at six weeks of life (WG from birth - week 6) were recorded. The WG proportion was measured at completed 4 and 6 weeks of life in relation to birth weight. It was calculated as the baby's

weight measured at 4 and 6 weeks of life minus birth weight, divided by birth weight. Other risk factors including birth weight, gestational age, gender, antenatal steroid therapy, use of oxygen therapy, initiation of enteral nutrition, parenteral nutrition duration, mechanical ventilation or nasal continuous positive airway pressure (CPAP) therapy, use of surfactant, and blood transfusions were recorded.

The chi-square test was used to compare the two groups. The WG proportion was included with the best discriminative sensibility/specificity value after the receiver operating characteristic (ROC) curve results as a cut-off point. 95% confidence interval and significance level of $p<0.05$ were recorded. Group 1 and Group 2 were scrutinized according to ROC curve cut-off point (the best value for sensibility and specificity), and the patients under this cut-off point were classified as low WG patients. There were no statistically significant differences in birth weights of the low WG and normal WG newborns according to ROC curve analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 17.0 for Windows, SPSS Inc., Chicago, IL, USA). The study protocol was approved by the Ethics Committee.

Results

This study was comprised of 126 neonates, of whom 72 (57.1%) were female and 54 (42.8%) were male. Mean birth weight and gestational age were 1162.3±200.4 g and 29.4±1.9 weeks, respectively, for Group 1 (no ROP/mild ROP) and 915.8±235 g and 26.8±2.3 weeks, respectively, for Group 2 (stage 3+ ROP group). Group 2 patients had significantly lower gestational age and lower birth weight.

The demographic characteristics of all patients and the risk factors for the development of ROP are demonstrated in Table I.

Weight gain and WG proportion at 4 and 6 weeks of life are shown in Table II ($p<0.05$). WG and WG proportion were significantly lower at the 6th week in Group 2. For the severity of ROP, the area under the ROC curve according to the WG proportion from birth to the 6th week of life was 0.63 (sensitivity and specificity values were 64% and 62%), and 54 patients were categorized in the low WG group. Table III demonstrates the relation of low WG proportion at the 6th week of life between Group 1 and Group 2. Group 1 had 92 patients, and 33 of them were in the area under the ROC curve <63.2 at the 6th week. Group 2 had 34 patients, and 21 were in the area under the ROC curve <63.2 at the 6th week.

Low weight, WG and WG proportion at the 4th and 6th weeks were the most predictive for ROP. ROC curve analysis revealed a cut-off <380 g WG in the first 6 weeks of life to have a sensitivity of 90% and specificity of 70%. WG proportion <42% in the first 6 weeks of life had a sensitivity of 78% and specificity of 62% for detection of severe ROP. Figure 1 demonstrates the relation of stage 3+ ROP and WG in all 126 patients.

Discussion

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that has been identified as one of the most important causes of preventable blindness among children in both developing and developed countries[4,5]. The risk factors for the development of ROP are low gestational age, low birth weight, respiratory distress syndrome, oxygen exposure, mechanical ventilation therapy, sepsis, intraventricular hemorrhage, and blood transfusions[6,8]. Long-term oxygen supplementation causes vasoconstriction of retinal vessels that leads to permanent damage[13]. Hyperoxia increases lipid peroxidation and leads to membrane damage[14]. During this study, all newborns were monitored, and the oxygen saturation target range was 88-92%. Another risk factor for ROP is blood transfusion, which causes an accumulation of iron, triggers lipid peroxidation and increases oxidative stress on the immature retina[15]. In our study, blood transfusions were significantly higher in the stage 3+ ROP group.

Recent studies have shown postnatal WG as an important and independent risk factor for stage 3+ ROP12. Postnatal growth factors may have a role in the pathogenesis and severity of ROP. Fetal insulin-like growth factor-1 (IGF-1) levels rapidly increase during the third trimester, and preterm infants have low serum concentrations of IGF-1 due to loss of maternal sources. Low concentrations of IGF-1 prevent normal retinal blood vessel growth. IGF-1 levels gradually increase with postnatal growth. Poor WG has

Table I. Demographic Characteristics and Risk Factors of the Two Groups

	No-ROP/Mild ROP (n: 92)	Stage 3+ ROP (n: 34)	p
Birth weight (g)	1162.39±200.4	915.88±235	*
Gestational age (weeks)	29.4±1.9	26.8±2.3	*
Gender (F/M), n	51/41	21/13	
Antenatal steroid, n (%)	57 (61.9%)	20 (58.8%)	>0.05
Surfactant therapy (%)	65 (70.6%)	33 (97%)	*
Oxygen therapy (days)	20.6±24.6	56.9±39.8	*
Mechanical ventilation therapy (days)	3.7±11.2	13.3±16.7	*
Nasal CPAP duration (days)	2±2.2	5±4.3	*
Transfusion, n (%)	71 (77.1%)	34 (100%)	*
Parenteral nutrition duration (days)	13.1±7.7	23.1±11.7	*
Initiation of enteral nutrition (days)	2.7±3.1	4.4±6.7	>0.05
Hospitalization (days)	41.6±18.1	76.7±28.2	*

*p<0.05

an important role in the development of ROP[16]. In our study, we divided preterm neonates into two groups according to the severity of ROP and determined that low WG and low WG proportion were important risk factors for stage 3+ ROP. When we analyzed 126 preterm infants, 54 newborns had a WG proportion lower than 63% according to the ROC curve, which was an independent risk factor for severe ROP. We compared 54 newborns (low WG) with 72 newborns (normal WG) whose birth weights were not statistically significantly different, but there were significant differences in weight, WG and WG proportion (at the 4th and 6th weeks). The area under the ROC curve was 63%. For the discriminative cut-off of 42% of WG proportion at the 6th week, sensitivity and specificity values were 78% and 62%. The cut-off value for WG at the 6th week was 380 g, and sensitivity and specificity values were 90% and 70%. In our study, preterms who gained ≤380 g or whose WG proportion was ≤42% had the highest risk for the development of ROP. Wallace et al.[10] showed that WG of <50% of their birth weight in the first 6 weeks of life was a risk factor for the development of severe ROP. In our study, postnatal poor WG at 6 weeks was a predictive factor for stage 3+ ROP. Another study investigating growth characteristics and the relation with ROP showed small for gestational age and birth weight <25th percentile to be risk factors for severe ROP.[11] In our study, when we analyzed all 126 infants with low birth weight (≤1500 g), we showed that poor postnatal WG was related to stage 3+ ROP.

Löfqvist et al.[17] showed that the WINROP (weight IGF-1 neonatal ROP) algorithm was predictive and had 100% sensitivity and 54% specificity for ROP development in 50 preterms at postnatal age of 26 weeks. Palmer et al.[18]

Table II. Weight gain (WG) and Weight Gain Proportion at 4 and 6 Weeks of Life in the Two Groups

	No ROP/Mild ROP (n: 92)	Stage3+ ROP (n: 34)	p
WG at 4th week (g)	408.4±185.3	218.5±146.8	*
WG proportion at 4th week (%)	37.5±19.6	26±17.6	*
WG at 6th week (g)	914.1±376.3	473.8±272	*
WG proportion at 6th week (%)	78.8±32.1	56.2±31.5	*

*p<0.05

Table III. Group 1 and Group 2 according to Low Weight Gain (the area under the ROC curve was 0.63) and ROP Severity

ROP	Area under ROC curve >63.2 at 6th week (n=72)	Area under ROC curve ≤63.2 at 6th week (n=54)	p
Group 1 (n=92)	59	33	*
Group 2 (n=34)	13	21	*
Total (n=126)	72	54	*

*p<0.05

showed the importance of low birth weight for the development of ROP. This study revealed that the risk of ROP for 1000-1250 g infants was 47%, for 750-999 g infants was 78%, and for <750 g infants was 90%. In a recent study, relative WG (g/kg/day) at two-week intervals until postnatal 6 weeks was evaluated among infants with ≤1500 g birth weight for the prediction of severe ROP. They found no difference at the 6th week, but showed that poor relative WG in the first 4 weeks was a predictor for severe ROP.[19] In our study group, 54 infants with low WG proportion had significantly highest risk for severe ROP. In this group, postnatal weight, WG, and WG proportion at the 4th and 6th weeks were predictive for severe ROP, but 6th week values had the highest sensitivity and specificity.

Enteral nutrition may influence serum IGF-1 and ω-3 fatty acid concentrations, which are known to be protective against ROP.[20,21] Porcelli et al.[22] showed that infants who require ROP treatment receive more parenteral nutrition and less human milk. There are several factors

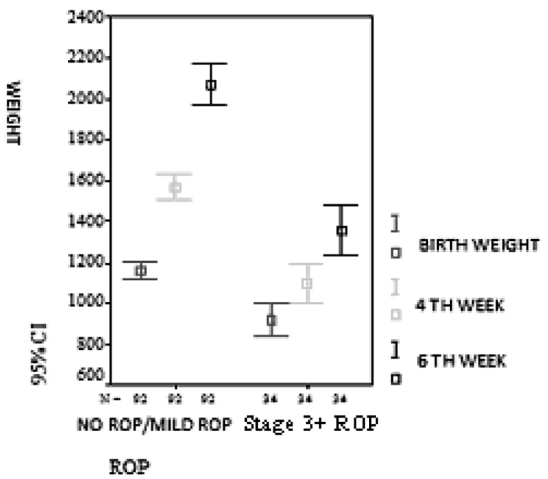

Fig. 1. Growth follow-up of the two groups.

that affect ROP, and the entity is associated with poor postnatal WG due to poor enteral nutrition, depletion of ω-3 fatty acids, and also with intrauterine infection and fluctuating oxygen levels.[20-24] In our study group, although there was no significant difference in receipt of their nutritional needs between the low WG group and the normal weight group (72 infants), the growth characteristics were significantly different, and this may be associated with the longer parenteral nutrition duration rather than enteral nutrition. Although we have demonstrated that duration of parenteral nutrition was longer in the patients with stage 3+ ROP, lack of evaluation of the duration of parenteral nutrition in the low WG and normal WG groups is the limitation of this study. A larger study showed a predictive role of WG for the risk of severe ROP, and it had a role in reducing the number of ROP examinations.[25] Gestational age and birth weight were used for ROP screening, but these were not the only risk factors for predicting treatment requirement in more than 90% of infants[1,26]. Wu et al.[27] showed that the use of WG analysis is useful for determining severe ROP. In another study, Wu et al.[12] emphasized that the WINROP algorithm and postnatal WG had 100% sensitivity and 81.7% specificity in detecting severe ROP.

In conclusion, our results suggest poor WG proportion and WG at the 4th and 6th weeks of life are predictors for stage 3+ ROP. Although nutrition type and birth weight were the same in the two groups, low WG proportion and WG were important risk factors for stage 3+ ROP. Ophthalmologists and neonatologists should closely follow preterm infants with respect to weight, WG and WG proportion at the 4th and 6th weeks of life in order to predict stage 3+ ROP.

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