·Clinical Research·

Postnatal weight gain in very low birth weight infants in Beijing and the risk of retinopathy of prematurity

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Abstract

• AIM: To analyze the low weight gain (WG) from birth to 4 and 6wk of life to predict the development of retinopathy of prematurity (ROP) among very low birth weight (VLBW) preterm babies.

• METHODS: Three hundred and three newborns with VLBW were analyzed. Body weight measurements were recorded weekly. In all patients, the proportion of the WG was defined as the preterm weight measured at the 4th and 6th weeks of life minus the birth weight (BW) divided by the BW. Other risk factors for ROP were also analyzed.

• RESULTS: Mean gestational age and mean BW of the whole cohort were 29.56±1.44wk and 1270.58±176.18 g respectively. WG proportion at 4wk postnatal age (18.89%±13.58%) were significantly lower in infants with ROP (P=0.003). WG proportion at 6wk was not different between ROP and no ROP group (42.48%±20.36% *vs* 46.43%±15.65% P=0.118). When all the other risk factors significant for ROP were included in the logistic regression poor WG did not arise as an independent risk factor. Area under the ROC curve was 0.591 (95% CI: 0.515-0.666; P=0.016). For ROP, the best discriminative cutoff of 18.06% of the proportional WG at the 4th week over the BW, sensitivity and specificity values were 67.3% and 50.0% respectively.

• CONCLUSION: Low WG proportion in the first 4wk of life is maybe an additional predictor of ROP in very low BW infants. Preterm babies with low BW and low WG proportion should be followed closely for ROP.

• **KEYWORDS:** retinopathy of prematurity; weight gain; risk factors; weight gain proportion
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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of preventable blindness in child in industrialized countries [1]. ROP is a multifactorial disease that occurs most frequently in very small and sick infants including low gestational age, low birth weight (BW), oxygen exposure, mechanical ventilation therapy, respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage, and blood transfusions [2-4]. There are few studies investigating the relationship between low weight gain (WG) and ROP [5-9]. There is no study addressing the importance of the very low BW (VLBW) infants' WG and the occurrence of ROP in China. We aimed to determine the role of postnatal WG in the development of ROP among VLBW infants.

SUBJECTS AND METHODS

Subjects In this study, preterm infants born with BW≤1500 g at Neonatal Intensive Care Units (NICUs) of Bayi Children's Hospital Affiliated to the Beijing General Hospital of the Chinese PLA, Beijing from January 1, 2012 to December 30, 2012 were recruited. Neonates with hydrocephalus, congenital anomalies, those who died or lost to follow-up before development of ROP requiring treatment or full vascularization of the retina were excluded. The study was approved by the Hospital Ethics Committee and confirmed forms were also assigned by the babies' parents or legal guardians before the initial screening.

Methods The infants were first examined at 4-6wk chronological age or 32wk corrected age to the 45th corrected gestational age (GA) by a senior ophthalmologist. Pupils were dilated with application of mydriatic eye drops (0.5% phenylephrine and 0.5% tropicamide), instilled fourth at an interval of 15min. The fundus was examined with a binocular indirect ophthalmoscope and +28 D lens, lid speculum, and scleral depressor approximately 45min after the first instillation. A drop of 0.4% oxybuprocaine was used for topical anesthesia. Infants were monitored until a diagnosis of ROP was established or eyes were fully vascularized. Staging of ROP was recorded according to the international classification of ROP [10]. If ROP developed, then parents were asked to sign a consent form to allow the more frequent examinations necessary to track the course

Table 1 Univariate analysis of risk factors for the development of ROP *n* (%), $\bar{x} \pm s$

Risk factors	ROP (*n*=80)	No ROP (*n*=223)	*P*
BW (g)	1170.13±192.38	1306.62±155.28	<0.001
GA (wk)	28.83±1.39	29.83±1.36	<0.001
Sex (M/F)	44/36	129/94	0.659
Respiratory distress syndrome	62 (77.50)	154 (69.06)	0.152
Patent ductus arteriosus	40 (50.00)	105 (47.08)	0.654
Intraventricular hemorrhage	19 (23.75)	28 (12.56)	0.018
Sepsis	15 (18.75)	34 (15.25)	0.465
1-min Apgar score <7	21 (26.25)	53 (23.77)	0.657
5-min Apgar score <7	13 (16.25)	24 (10.76)	0.198
Mechanical ventilation duration(d)	5.49±6.52	2.57±3.42	<0.001
Nasal CPAP duration (d)	8.49±9.97	4.59±5.77	<0.001
Dexamethasone treatment	66 (82.50)	185 (82.96)	0.925
Surfactant treatment	61 (76.25)	145 (65.02)	0.065
Blood transfusion	70 (87.50)	192 (86.10)	0.753
Anaemia	66 (82.50)	172 (77.13)	0.315
Meningitis	4 (5.00)	5 (2.24)	0.388
WG at 4th week (g)	221.13±166.58	307.30±152.16	<0.001
WG at 6th week (g)	487. 63±223.93	597.91±189.56	<0.001
WG proportion at 4th week (%)	18.89±13.58	23.93±12.53	0.003
WG proportion at 6th week (%)	42.48 ±20.36	46.43±15.65	0.118

BW: Birth weight; GA: Gestational age; CPAP: Continuous positive airway pressure; WG: Weight gain.

and severity of ROP. The criteria for treatment were: zone I any stage of ROP with plus disease or zone I stage 3 without plus and zone 2 stage 2 or 3 with plus disease as defined by Early Treatment for ROP Cooperative Group [11]. Patients were divided in to two groups as having no ROP and ROP.

Baby's weights measurements weekly up to 6wk chronological age were recorded. Relative WGs (body weight minus BW divided by BW) at fourth, and sixth week were calculated. Neonatal characteristics also recorded for each neonate included gestational age, BW, gender, 1,5-min Apgar score, postnatal steroid therapy, surfactant treatment, mechanical ventilation, nasal continuous positive airway pressure (CPAP) duration, RDS, patent ductus arteriosus (PDA), culture proven sepsis, intraventricular hemorrhage (IVH), and blood transfusion.

Statistical Analysis Analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The results are presented as numbers (*n*), frequencies (%), means with respective standard deviation (SD). The Chi-square test was used to compare no-ROP patients and ROP patients. Student's unpaired *t*-test was used to compare continuous data. In the logistic regression, the dependent variables were chosen by their significance after univariate analysis. Backward stepwise method was used in logistic regression. Odds ratios and 95% confidence intervals (CI) for each risk factor were determined. Receiver operating characteristic (ROC) curve was used for determination of the best discriminative cut-off of relative WG at fourth week of life to predict ROP. All reported *P*-values are two-sided, and $P<0.05$ were considered statistically significant.

RESULTS

During the study period, a total of 303 premature pairs were delivered at our NICUs. One hundred and seventy- three (57.10%) of whom were male. The mean GA of the cohort was 29.56±1.44wk (range 26.0-33.0wk), and the mean BW was 1270.58±176.18 g (range 770-1500 g). The prevalence of any stage ROP in our sample was 80 infants (26.40%), including 67 (22.11%) with mild ROP was defined as the ROP that did not meet the criteria for treatment and 13 (4.29%) with severe ROP defined as that needed treatment. Mean BW and GA were 1170.13±192.38 g (range 770-1500 g) and 28.83±1.39wk (range 26-32wk), respectively for the ROP group and 1306.62±155.28 g (range 900-1500 g) and 29.83± 1.36wk (range 26-33wk) respectively, for the no ROP group. Patients with ROP had significantly lower BW and GA compared with those with no ROP. Relative WG at fourth week of life were significantly lower in infants with ROP ($P=0.003$). Relative WG at fourth and six week of life were significantly lower in infants with ROP ($P<0.001$). The WG proportion in the first 4wk of life in ROP group was 18.89%±13.58%, compared with 23.93%±12.53% for those without ROP ($P=0.003$). The WG proportion at sixth week was not different between groups ($P=0.118$). The demographic characteristics of all patients and the risk factors for the development of ROP are demonstrated in Table 1.

All the risk factors found to be significant in univariate analysis were put in to a logistic regression model, BW (P< 0.001), GA (P=0.024), mechanical ventilation duration (P= 0.017) were independent risk factors for ROP and poor WG, nasal CPAP duration and IVH did not arise as an independent risk factor at this model (Table 2).

For ROP, the area under the ROC curve according to the WG proportion from birth to the 4th week of life was 0.591 (95% CI: 0.515-0.666; P =0.016). ROC curve analysis revealed the best discriminative cutoff of 18.06% of the proportional WG at the 4th week over the BW, sensitivity and specificity values were 67.3% and 50.0% respectively. We divided the cohort into two groups as low WG and high WG groups using 18.06% of the proportional WG cut-off. One hundred and fourteen patients were categorized in the low WG group, 40 patients had ROP. One hundred and eighty-nine patients were in the high WG proportion group and 40 patients had ROP (Table 3, P =0.008). In our study group, the infants with low WG proportion had significantly higher risk for ROP.

Table 2 Independent risk factors for ROP

Independent risk factors	Adjusted odds ratio	95% CI	P
BW	-0.004	0.994-0.998	<0.001
GA	-0.275	0.598-0.964	0.024
Mechanical ventilation duration	0.088	1.016-1.173	0.017

BW: Birth weight; GA: Gestational age.

Table 3 ROP and no ROP patients according to low WG

Groups	High WG	Low WG
ROP	40	40
No ROP	149	74
Total (303)	189	114

ROP: Retinopathy of prematurity; WG: Weight gain. P=0.008.

DISCUSSION

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 [12,13]. Gilbert *et al* [13] suggested that ROP prevails among preterm infants weighing less than 1000 g at birth in industrialized countries and has emerged as a major cause of childhood blindness in developing countries due to a sharp increase in the survival of VLBW preterm infants [14]. Although these figures vary greatly among countries, survival rates of infants between 27 and 28wk' GA at birth have been reported to reach approximately 90% [15]. ROP pathogenesis is still incompletely understood. Although oxygen use, low GA and low BW are major risk factors for ROP, other factors reflecting the postnatal changes in the overall health of the baby, such as RDS, sepsis, IVH, and blood transfusion are also positively associated with ROP development[2,3,16]. Christiansen *et al* [17] reported a significant association between IVH and ROP in 60 VLBW where neonates with more severe IVH grades reached severe ROP. In our study, gender, 1,5-min Apgar score, postnatal steroid therapy, surfactant treatment, RDS, PDA, culture proven sepsis, meningitis, and blood transfusion were not significantly different between the two groups. We found that the IVH were significantly higher in the ROP group and low GA, low BW, low WG proportion at 4th week were the risk factors of ROP.

Current screening guidelines for ROP use only GA and BW as criteria and do not take postnatal factors into consideration. Postnatal growth factors may have a role in the pathogenesis and severity of ROP. Poor postnatal WG as a risk factor for ROP development was described recently[5-7]. Wallace *et al* [6] reported that GA and poor relative WG in the first 6wk of life were independent risk factors for stage 3 ROP. They suggested that WG under 50% of BW at 6wk of life indicated an important risk for severe forms of ROP. Fortes Filho *et al*[5] reported that low WG proportion (baby's weight measured at 6wk of life minus the BW, divided by the BW) under 51.2% of the BW at 6wk can predict severe ROP with a sensitivity of 66.3% and specificity of 62.6% in VLBW infants. A recent study, relative WG [g/(kg•d)] at 2wk intervals until postnatal 6wk was evaluated among infants with VLBW for the prediction of severe ROP. They found no difference at the 6th week, but showed that poor relative WG in the first 4wk was a predictor for severe ROP[18]. They revealed a cut-off of 9.1 g/(kg•d) WG in the first 4wk of life with a sensitivity of 76.2% and specificity of 50.4% for detection of ROP requiring treatment. In our study, we found that the WG and WG proportion at 4wk postnatal age were significantly lower in infants with ROP (P<0.001, P=0.003 respectively) and the WG at 6wk were also significantly lower in infants with ROP (P <0.001). But the WG proportion at 6wk were no difference between groups (P = 0.0118). There were only 13 patients with severe ROP, so additional research including larger number of severe ROP is required in future. For ROP, receiver operating curve analysis that the area under the ROC curve was 59.1% according to the WG proportion from birth to the 4th week of life. For the discriminative cut-off of 18.06% of WG proportion at the 4th week, sensitivity and specificity values were 67.3% and 50.0%. Most of the morbidities related to prematurity are experienced in the first month of life and poor WG is strongly associated with the morbidities. So this may explain why poor WG at 4wk postnatal age is better correlated with ROP than that at 6wk[18].

A larger study showed a predictive role of WG for the risk of ROP, and it had a role in reducing the number of ROP examinations [19]. In our study, we divided preterm neonates into two groups according to the discriminative cut-off of 18.06% of WG proportion at the 4th week, 114 infants with low WG proportion had significantly higher risk for ROP (35.09% *vs* 21.16%, P =0.008). Recently, some studies

showed the relation between the insulin-like growth factor-I (IGF-1) and ROP development. Lofqvist *et al*[9] showed that that weekly measurements of postnatal WG together with a serum level of IGF-1 were a useful marker for the risk of severe ROP. Fetal 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 [20]. The maternal factors, postnatal nutrition and the WG can regulate the concentrations of serum IGF-1 among preterm infants [21]. IGF-1 is present in the natural maternal milk[22], and so an adequate natural breast-feeding could help in the prevention of ROP.

When all the risk factors significant for ROP in univariate analysis were included in the logistic regression, poor postnatal WG did not arise as an independent risk factor. The BW, GA and mechanical ventilation duration were independent risk factors for ROP. We believe that poor WG is strongly associated with other risk factors in this model, therefore lost significance in logistic regression. So poor relative WG in the first 4wk of life is a predictor for ROP, but not an independent risk factor. It can help to identify infants with poor postnatal course and are at greater risk, but cannot be used as a screening tool alone. Ophthalmologists should closely follow preterm infants with respect to BW, GA, mechanical ventilation duration and WG proportion at the 4th week of life in order to predict ROP.

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