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PEDIATRICS

Weight gain measured at 6 weeks after birth as a predictor for severe retinopathy of prematurity: study with 317 very low birth weight preterm babies

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Abstract
Background Recent studies suggest that postnatal weight gain can play an important role in the development of retinopathy of prematurity (ROP).
Aim To analyze the low weight gain (WG) from birth to 6 weeks of life to predict the development of severe retinopathy of prematurity (ROP) among very low birth weight preterm babies (VLBW).
Methods A prospective cohort study included 317 newborns with birth weight (BW) ≤1,500 g and gestational age (GA) ≤32 weeks. The main outcome was the development of severe ROP (defined as threshold ROP and higher stages of ROP). In all patients, the proportion of the WG was defined as the preterm weight measured at 6 weeks of life minus the BW divided by the BW. Seventeen risk factors for ROP were studied by univariate analysis. Chi-square test and Student's *t*-test were used to compare no-ROP/mild ROP patients and severe ROP patients. Logistic regression and receiver operating characteristic (ROC) curve were used to determine if the WG proportion was independently related to severe ROP development and if it was capable of predicting severe ROP. Ophthalmological examinations started between the fourth and sixth week of life, and were repeated until the 45th week of postmenstrual age. Weight gain proportion was always calculated at completed 6 weeks of life.
Results Mean GA and mean BW of the whole cohort were 29.6 weeks (±1.9) and 1,124 grams (±239.5) respectively. After logistic regression, the low WG proportion under 51.2% from the BW, measured at 6 weeks of life, showed OR 3.007 (95%CI: 1.195-7.566; P=0.019), for severe ROP, when adjusted for BW and for any stage intraventricular hemorrhage. Area under the ROC curve was 0.63 (95%CI: 0.495-0.761; P=0.037). For the discriminative cutoff of 51.2% of the WG proportion, sensitivity and specificity values were 66.3% and 62.6% respectively. Positive and negative predictive values were 10.2% and 94.7% respectively.
Conclusions Low WG by six weeks of life is an important and independent risk factor for severe ROP and is capable to predict the development of severe ROP in most patients that needed treatment.

Keywords Retinopathy of prematurity · Risk factors · Weight gain · Prevalence · VLBW infants

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Introduction

Retinopathy of prematurity (ROP) is an important complication of preterm newborns. ROP was first described in 1942, and quickly became a leading cause of childhood blindness in industrialized countries [1]. Recently, ROP has been also identified as one of the most important causes of treatable blindness among children in many countries in

Latin America, China and India and among the former emerging economies from East Europe, due to the increase in the survival rates among preterm newborns [2, 3].

ROP is a multifactorial disease, and the main postnatal risk factors described are oxygen-therapy, low gestational age (GA), low birth weight (BW), sepsis, intraventricular hemorrhage, blood transfusion, and use of indomethacin, surfactant and erythropoietin [4–6].

Postnatal low weight gain (WG) of very low birth weight (VLBW) infants is a recently mentioned risk factor for ROP [7–9]. Only three previous studies, a retrospective [7], a case-control [8], and a prospective cohort [9], reported the association between postnatal low WG and occurrence of ROP in VLBW premature infants. In the last of these studies, Löfqvist et al. [9] demonstrated the usefulness of the longitudinal postnatal WG and serum insulin-like growth factor-I (IGF-I) measurements from birth until postmenstrual age of 36 weeks to predict ROP. There is no prospective study addressing only the importance of the VLBW infants' WG and the occurrence of severe ROP. In the year 2002, we designed a prospective cohort study to analyze if the WG from birth to 6 weeks of life could be an independent risk factor for severe ROP and if it could predict severe ROP, once the low postnatal WG is easily identifiable as a risk factor, during the screening sessions to detect ROP.

Methods

Patients

We performed a prospective cohort study analyzing the prevalence of severe ROP from the initial ophthalmologic examination up to the 45th week of postmenstrual age and the WG proportion from birth up to 6 weeks of life. All preterm neonates admitted to the Neonatal Intensive Care Unit (NICU) of Hospital de Clínicas de Porto Alegre, Brazil from October 2002 to November 2007, with BW ≤1,500 grams and GA ≤32 weeks, were included. Infants that died before completing 6 weeks of life or before 45 weeks of postmenstrual age were excluded. No other exclusion criteria were used. The ophthalmic examination was always performed by the same author (JBFF) and consisted of binocular indirect ophthalmoscopy with a 28 D Nikon lens (Nikon®, Melville, NY, USA) and the lid speculum for newborn (Alfonso Eye Speculum, Storz®, Bausch & Lomb Inc., San Dimas, CA, USA), after dilation of the pupils with eye drops containing tropicamide 0.5% and phenylephrine 2.5%. Scleral indentation was used in order to achieve a better examination of the peripheral zone III.

According to the Brazilian guidelines for ROP screening, all infants were first examined between 4 and 6 weeks of life and then followed once or twice a week depending on the severity of the disease or until retinal vascularization was completed. All babies were allways examined in the NICU while hospitalized, and as outpatients after discharge up to completed 45 weeks of postmenstrual age.

Outcome and variables

The main clinical outcome was the occurrence of severe ROP in either eye during the entire observational period. The worst ROP stage, in either eye, was always recorded, according to the International Classification of 1984/1987 [10, 11]. Severe ROP was defined as any ROP stage 3, threshold disease, or more. Threshold disease was defined according to the Multicenter Trial of Cryotherapy for ROP [12]. The prevalence of ROP was calculated with 95% confidence intervals.

The main variable was the WG proportion measured at completed 6 weeks of life in relation to BW. It was calculated as the baby's weight measured at 6 weeks of life minus the BW, divided by the BW, in all patients. Perinatal variables considered for the study were the already described risk factors for ROP: BW, GA, gender, use of oxygen-therapy on mechanical ventilation or on nasal Continuous positive airway pressure (CPAP), single or multiple gestation, use of surfactant, indomethacin and erythropoietin therapies, Apgar score at 5 minutes, sepsis, meningitis, all intraventricular hemorrhage stages, blood transfusions, persistent ductus arteriosus, weight at 6 weeks of life, and the absolute WG at 6 weeks of life (defined as the baby's weight at completed 6 weeks of life minus the BW). Those data were obtained prospectively.

Statistical methods and ethics

The chi-square test was used to compare no-ROP/mild ROP patients and severe 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. The main variable (WG proportion from birth to the sixth week of life) was included in the logistic regression as a continuous variable, without cutoff points, as well as it was included with the best discriminative sensibility/specificity value after the ROC curve results as a cutoff point. Patients under this cutoff point were classified as low WG patients. Odds ratio (OR) was calculated and compared after adjustments in both situations. Confidence interval 95% and significance level of $P<0.05$ were recorded. Receiver operating characteristic (ROC) curve was calculated for the proportional WG and severe ROP development. Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 14.0 for Windows, SPSS Inc., Chicago, IL,

USA). The study protocol was approved by the Ethics Committee of the HCPA.

Results

The prospective cohort comprised 317 neonates, of whom 183 (57.7%) were female and 63.7% were small for GA (SGA <10 percentile) patients. Birth weight in all studied newborns ranged from 505 to 1,500 grams, with a mean of 1,124 grams (SD 239.5). Gestational age ranged from 24 to 32 weeks, with a mean of 29.7 weeks (SD 1.9). Severe ROP needing treatment occurred in 24 patients (7.2%), among whom 23 achieved ROP stage 3, threshold disease and were treated by transpupillary diode laser photocoagulation. One patient reached ROP stage 4 despite two laser treatments. Only one patient reached ROP stage 5 (0.3%) by missing the scheduled treatment after NICU discharge, and only one baby, born at 32 weeks GA and with BW of 1,315 grams, developed ROP (threshold disease) at postmenstrual age of 41 weeks. This baby achieved 2,200 grams by the sixth week of life (with 68% of the WG proportion, as defined). The mean GA for pre-threshold ROP among our patients was 36.3 (SD 1.6) weeks and for threshold ROP was 37.9 (SD 1.7) weeks. The demographic characteristics of all included patients, as well as the complete prevalence of ROP, are displayed in Table 1.

In Table 2 we show the univariate comparison between no-ROP/mild ROP and severe ROP patients: BW ($P<0.001$), GA ($P<0.001$), weight at 6 weeks of life ($P<0.001$), WG ($P<0.001$), WG proportion ($P=0.019$), and any stage intraventricular hemorrhage ($P=0.047$) were significantly lower in severe ROP patients.

Table 1 Prevalence of ROP and demographic characteristics of the study population

Characteristic	Value
Number of patients	317
No-ROP	219 (69.1%)
ROP	98 (30.9%)
ROP 1	42 (13.2%)
ROP 2	32 (10.1%)
ROP 3*	22 (6.9%)
ROP 4*	1 (0.3%)
ROP 5*	1 (0.3%)
Female gender	183 (57.7%)
SGA	202 (63.7%)
Mean BW (grams)**	1,124.0±239.5
Mean GA (weeks)**	29.6±1.9
Mean WG (grams)**	597.0±218.1

*: Severe ROP needing treatment; **: Data presented as mean ± standard deviation; SGA: small for the gestational age (<10 percentile); BW: birth weight; GA: gestational age; WG: weight gain from birth to the sixth week of life.

After logistic regression, the WG proportion from birth to the sixth week of life, adjusted for BW and for any stage intraventricular hemorrhage, showed OR 3.007 (95%CI: 1.195-7.566; $P=0.019$) when considered the cutoff point under 51.2% of the BW; and as a continuous variable, without cutoff points, it showed OR 1.032 (95%CI: 1.008-1.055; $P=0.008$), Table 3.

For severe ROP, the area under the ROC curve was 0.63 (95%CI: 0.495-0.761; $P=0.037$). For the best discriminative cutoff of 51.2% of the proportional WG over the BW, sensitivity and specificity values were 66.3% and 62.6% respectively. Positive and negative predictive values were 10.2% (95%CI: 6.1-15.9%) and 94.7% (95%CI: 90.5-97.4%) respectively.

Discussion

Our study showed that WG proportion under 51.2% from birth to 6 weeks of life was an important and independent risk factor for severe ROP, and was capable of predicting the development of severe ROP needing treatment in the group of VLBW preterm babies. Our results are also in accordance with the longitudinal growth curves for hospitalized VLBW described by Ehrenkranz et al. [13] in 1999, and widely used in modern neonatology, in which these patients are expected to regain weight, around 50% of their BW, after completed 6 weeks of life.

ROP pathogenesis is still incompletely understood. For many years, the high oxygen levels administered to neonates was considered the main risk factor for ROP development [14]; however, the disease kept occurring even after careful control in oxygen administration [15]. To date, no absolutely safe level for oxygen use has been demonstrated [16, 17]. In our institution, oxygen administration is always monitored by pulse oxymetry, with recommended saturation between 88-94%. The overall incidence of ROP in our study was similar to other published results [18–20].

The presence of any stage intraventricular hemorrhage was significant as a risk factor for ROP in our cohort of patients. Procianoy et al. [21], in 1981, related a significant association between cicatricial ROP and intraventricular hemorrhage in 138 VLBW. Christiansen et al. [22], in 2002, published a significant association between intraventricular hemorrhage and ROP in 60 VLBW where neonates with more severe intraventricular hemorrhage grades reached severe ROP.

Low BW and GA have been implicated most directly in ROP development [23–25], but low WG as an independent risk factor for ROP development was just recently

Table 2 Univariate analysis of the risk factors for the development of severe ROP

	No-ROP/Mild-ROP patients (n=293)	Severe ROP patients (n=24)	P
Birth weight (grams) *	1,141.6±231.7	908.7±232.6	<0.001
Gestational age (weeks) *	29.8±1.8	27.9±2.2	<0.001
Weight at 6 weeks of life (grams) *	1,753.9±362.5	1,319.2±419.7	<0.001
Weight gain (grams) *	612.3±205.6	410.4±279.1	<0.001
Weight gain proportion (%)*	54.6±18.3	45,1±25.1	0.019
Apgar score at 5 minutes*	7.8±1.7	7.6±1.7	0.653
Use of oxygen on mechanical ventilation	152 (52.1%)	15 (62.5%)	0.397
Use of oxygen on nasal CPAP	230 (78.5%)	20 (83.3%)	0.795
Use of erythropoietin	231 (79.1%)	20 (83.3%)	0.819
Use of indomethacin	100 (34.1%)	9 (37.5%)	0.824
Any intraventricular hemorrhage stage	45 (15.4%)	8 (33.3%)	0.047
Blood transfusions	129 (44.0%)	14 (58.3%)	0.204
Use of surfactant	140 (47.8%)	14 (58.3%)	0.397
Multiple gestation	46 (15.7%)	4 (16.7%)	1.000
Sepsis	200 (68.3%)	19 (79.2%)	0.360
Meningitis	19 (6.5%)	3 (12.5%)	0.486
Persistent ductus arteriosus	40 (13.7%)	3 (12.5%)	1.000
Female gender	170 (58.0%)	13 (54.2%)	0.830

*Data presented in mean ± standard deviation (Student's t-test); BW: birth weight; nasal CPAP: nasal continuous positive airway pressure

described. Hall et al. [26], in 1995, related a low WG associated with severity of ROP in four survivors in a birth of quintuples with identical GA and similar BW. Homes and Düffner [27], in 1996, demonstrated that rats submitted to growth retardation developed retinal neovascularization more frequently and more severely.

A retrospective study by Wallace et al. [7], published in 2000, analyzed postnatal WG and another 11 risk factors in a group of 111 neonates. They suggested that WG under 50% of BW at 6 weeks of life indicated an important risk for severe forms of ROP. According to Wallace et al., the study results could not be explained by the difference in the average BW among the patients with severe ROP and those with less severe or no ROP, but by the difference in WG proportion in the 6-week period after premature birth, and they concluded that there was a significant difference in WG in infants with severe and discrete or no ROP. Shaffer et al. [28] previously claimed that the absolute ratio of WG in VLBW would be proportional to the neonate's BW, and consequently, the expected proportion of WG should be the same for preterm infants with different BW in the same period of life.

Allegaert et al. [8], in 2003, in a prospective case-control study registered perinatal growth characteristics of 31 neonates with ROP threshold disease and in 31 neonates with the same GA who didn't develop ROP. They concluded that small for GA preterm newborns and those with intrauterine growth restriction had an increased risk of developing ROP threshold disease. In contrast, the relative WG (grams/kg/day) was not significantly different in the group with ROP and in the control group.

Recently, some studies showed the relation between the insulin-like growth factor-I (IGF-I) and ROP development. Hellström et al. [29] reported that in preterm infants with the same GA, IGF-I serum levels during the postnatal period were significantly and proportionally lower in those that developed ROP than in the ones who did not. In 2006, Löfqvist et al. [9] showed that weekly measurements of postnatal WG together with a serum level of IGF-I were a useful marker for the risk of severe ROP. In this article, the authors disclosed some very important conclusions indicating the need to monitor the postnatal factors of weight, IGF-I level and IGF binding protein 3 level in order to enhance the clinician's ability to identify patients who will require treatment for ROP. Unfortunately, this approach seems to have some difficulties of use among ophthalmologists during the screening sessions to detect ROP, mainly in the middle-income countries context; once-weekly

Table 3 Odds ratio to develop severe ROP after logistic regression adjusted when a weight gain proportion is used as a continuous variable, and the weight gain proportion under 51.2% of the birth weight, according to the ROC curve

	OR	95% CI	P
Continuous WG proportion (without cutoffs)*	1.032	1.008 - 1.055	0.008
Low WG proportion* (WG <51.2% of the BW)	3.007	1.195 - 7.566	0.019

WG: weight gain; *: adjusted for birth weight (BW) and for any stage intraventricular hemorrhage.

laboratory measurements of IGF-I and IGF binding protein 3 serum levels are cost expensive for national health care systems, and also, these laboratory tools are not widely available in most of the Latin American countries.

Engström et al. [30] related the role of maternal factors, postnatal nutrition and the WG in regulation of serum IGF-I among preterm infants. IGF-I is present in the natural maternal milk, and so an adequate natural breast-feeding could help in the prevention of ROP.

A question beyond the scope of our study is about why these babies are poor at gaining weight. The most practical answer to this question could be because they are sicker babies; but once we know about low WG as a risk factor for ROP, it is possible to follow-up these babies closely before the development of treatable ROP, trying to improve their clinical conditions. According to Ehrenkranz et al. [13], the WG after the second week of life is related to the nutritional support, and healthier babies usually gain weight faster than sicker babies. The low WG in the postnatal period could be indicative for the development of general morbidities, some of them also related with ROP development, such as sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia, or necrotizing enterocolitis.

Our study aimed to prospectively analyze a cohort of patients with an adequate number of VLBW infants to determine if the proportion of postnatal WG is a risk factor for ROP development. After logistic regression, our results showed that WG proportion lower than 51.2%, according to the ROC curve, was an independent risk factor for severe ROP development. Furthermore, our study showed that all of the three variables related to the WG (weight at 6 weeks of life, absolute WG, and WG proportion from birth to 6 weeks of life) achieved statistical significance after univariate analysis. The area under the ROC curve in our study was 0.63 (95%CI: 0.495-0.761; P=0.037). For the discriminative cutoff of 51.2% of the WG proportion, sensitivity and specificity values were 66.3% and 62.6% respectively. Positive and negative predictive values were 10.2% and 94.7% respectively, thus meaning that a preterm who has gained more than 51.2% of weight proportional to his BW, at the end of the sixth week of life, has around 94.7% chance of not developing severe ROP.

Conclusions

Our results have clinical importance because low WG, as defined and measured at the end of 6 weeks of life, was an easy identifiable risk factor, and helpful for predicting severe ROP some weeks in advance of the development of treatable ROP. In this way, ophthalmologists and neonatologists should take special care, and pay attention to this group of patients during the screening for ROP. There is a need for more studies assessing improvements in nutrition among VLBW preterm babies at risk for ROP to better understand this factor in ROP development.

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