

Incidence and Main Risk Factors for Severe Retinopathy of Prematurity in Infants Weighing Less Than 1000 Grams in Brazil

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Summary

Objectives: This study evaluated the incidence and risk factors for severe retinopathy of prematurity (ROP) in babies <1000 g at Porto Alegre, Brazil.

Methods: Prospective cohort study including premature children with birth weight ≤ 1000 g was conducted. Main outcome was the occurrence of severe ROP needing treatment.

Results: A total of 157 infants were included. Severe ROP occurred in 20 infants (12.7%). Nineteen patients were treated by laser photocoagulation. Main risk factors for severe ROP were gestational age ($P = 0.029$), infant's weight measured at sixth week of life ($P < 0.001$) and number of days of oxygen therapy under mechanical ventilation ($P < 0.001$). After logistic regression, infant's weight at sixth week of life and number of days in mechanical ventilation were associated to severe ROP.

Conclusions: We reported the incidence of 12.7% of severe ROP among babies born ≤ 1000 g in our institution. Laser photocoagulation was effective to stabilize the disease among 19 treated patients.

Key words: Prematurity, retinopathy of prematurity, incidence, risk factors, blindness, prevention.

Introduction

Neonatal intensive care has improved during the past decade, resulting in a worldwide increase in survival of population of extremely low birth weight [ELBW; defined as birth weight (BW) ≤ 1000 g or 23–25 weeks gestational age (GA)] [1]. The ELBW preterm neonates are a highly vulnerable group of patients needing much attention from the Neonatal Intensive Care Unit (NICU) staff to detect postnatal morbidities and to minimize avoidable consequences

such as sepsis, meningitis, bronchopulmonary dysplasia, intraventricular hemorrhage, leukomalacia, persistent ductus arteriosus and retinopathy of prematurity (ROP).

ROP is the major cause of preventable childhood blindness and is a worldwide disease under constant investigation owing to the recent increasing survival of ELBW premature infants in many of the middle-income countries, among them, Brazil [2, 3].

ROP develops, most frequently, in the smallest and sickest preterm babies [4, 5]. There are reports of high incidence of severe ROP among ELBW [6–8], and there are controversies whether increasing survival of ELBW infants in the Latin American countries have also caused an increase in the occurrence of severe ROP in these patients [9]. Controversies concerning adequate time for initial ophthalmological screening in this subgroup of preterm infants were previously found to be related [1, 10–13]. In 2013, a new statement of the American Academy of Pediatrics Section on Ophthalmology, American

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Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus and American Association of Certified Orthoptists recommended the initial eye examination for preterm babies born with GA < 25 weeks at completion of 31 weeks of postconceptional age (PCA) [14].

This study aims to evaluate the incidence and main risk factors for severe ROP among ELBW preterm babies in Southern Brazil.

Methods

Study design and setting

A prospective cohort study was performed in preterm infants admitted to the NICU of the Hospital de Clínicas de Porto Alegre (HCPA), a tertiary university hospital in an urban area with a population estimated at 3 million inhabitants in Southern Brazil, from October 2002 to December 2012.

Patients and ophthalmological examination

All preterm infants with BW \leq 1000 g were included, except for those infants that died during hospitalization before the first ophthalmological examination. Patients were examined according to the Brazilian Guidelines to detect ROP [15]. The ophthalmological examination consisted of binocular indirect ophthalmoscopy after the dilation of pupils with eye drops association of tropicamide 0.5% and phenylephrine 2.5%. Infants were first examined between fourth and sixth week of life. Patients with incomplete peripheral retinal vascularization were followed up every 2 weeks until the 42nd week of PCA. Staging of the disease was according to the International Classification of ROP from 1984/1987 revisited in 2005 [16–18]. Patients with severe ROP were treated at threshold disease according to the Cryo-ROP [19] or at pre-threshold type 1 ROP according to the Early Treatment of Retinopathy of Prematurity study (ET-ROP) [20].

Outcomes and variables

The main clinical outcome was the occurrence of severe ROP (defined as ROP stage 3 plus, ROP stages 4 or 5) in either eye during the entire observational period. The worst stage of ROP was recorded.

The recorded variables were BW, GA (evaluated by obstetric history, early obstetric ultrasound and confirmed by newborn clinical examination), gender, being appropriate or small for GA (SGA; <10th percentile for GA), gemelarity (born from single or multiple gestation), patient's weight measured at completion of sixth week of life, use of oxygen therapy on mechanical ventilation or on nasal continuous positive airway pressure (CPAP), number of days on mechanical ventilation, use of surfactant, indomethacin, blood transfusions and erythropoietin therapies, occurrence of sepsis,

meningitis, all stages of intraventricular hemorrhage (IVH) and persistent ductus arteriosus (PDA). Sepsis, meningitis and IVH were diagnosed by clinical examination, microbiological culture and cranial ultrasound, respectively. The diagnosis of clinical sepsis was based on the occurrence of three or more of the following: apnea, difficult breathing, cyanosis, tachycardia or bradycardia, perfusion deficit or shock, irritability, lethargy, hypotonia and seizures, abdominal distention, vomits, dietary intolerance, gastric residue, hepatomegaly, idiopathic jaundice, thermal instability, petechiae or purpura and a general poor appearance. These data were obtained prospectively.

Statistical and ethics

The chi-square test was used to compare no-ROP patients (including in this group mild ROP patients, as stage 1 and stage 2) with severe ROP patients. Student's unpaired *t*-test was used to compare continuous data. Logistic regression was performed to the variables with significance after univariate analysis. Confidence interval 95% and significance levels of $P < 0.05$ were recorded.

All data were processed in the software SPSS 15.0® (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). The study protocol was approved by the ethics committee of the HCPA.

Results

A total of 157 infants were included. Mean BW and GA for the entire cohort were 844.04 ± 116.03 g (range 505–1000 g) and 28.3 ± 2.0 weeks (range 24–32 weeks), respectively. A total of 85 infants (54.1%) were SGA, 92 were female (58.6%) and 22 infants (14%) were natural twins. From the entire cohort, 99 patients (63.1%) developed clinical sepsis, 91 patients (58.0%) used oxygen therapy in mechanical ventilation, 89 patients (56.7%) received surfactant, 88 patients (56.1%) received erythropoietin, 49 patients (31.2%) developed any stage of IVH (15 patients with stages 3 or 4 of IVH) and 23 patients (14.6%) developed PDA. The mean weight of the entire cohort at completion of the sixth week of life was 1339.7 ± 279.14 g.

A total of 99 patients (63.15%) did not develop any stage of ROP. Seventeen patients (10.8%) developed stage 1 of ROP, and 21 patients (13.4%) developed stage 2 of ROP. Severe ROP in zone II occurred in 20 infants (12.7%). Mean BW and GA among patients with severe ROP were 808.75 ± 115.5 g and 27.4 ± 2.0 weeks, respectively. No patient achieved ROP in zone I or aggressive posterior ROP (AP-ROP). Nineteen patients were treated by diode laser photocoagulation. One outpatient at the 37th PCA lost the opportunity for laser treatment by missing follow-up appointment and the disease progressed to stage 5 of ROP and blindness.

TABLE 1
Incidence of ROP in patients with BW \leq 1000 g

ROP	Number of patients (%)
No-ROP/Mild ROP patients	137 (87.3%)
ROP 0	99 (63.1%)
ROP 1	17 (10.8%)
ROP 2	21 (13.4%)
Severe ROP patients	20 (12.7%)
ROP 3	18 (11.5%)
ROP 4	1 (0.6%)
ROP 5	1 (0.6%)
Total number of screened patients	157 (100%)

ROP, retinopathy of prematurity; BW, birth weight.

The mean PCA at diagnosis was 35.0 ± 1.9 weeks, and the mean PCA at treatment was 37.4 ± 1.8 weeks. The complete incidence of ROP is displayed in Table 1.

After univariate analysis, the main risk factors for severe ROP were GA at birth ($P=0.029$), patient's weight at sixth week of life ($P < 0.001$) and number of days of oxygen therapy under mechanical ventilation ($P < 0.001$). The recorded variables BW ($P=0.146$), need for blood transfusion ($P=0.077$), being SGA ($P=0.422$), gender ($P=1.000$), gemelarity ($P=1.000$), use of CPAP ($P=0.738$), use of mechanical ventilation ($P=0.256$), use of indomethacin ($P=1.000$), use of surfactant ($P=1.000$), use of erythropoietin ($P=0.285$), occurrences of sepsis ($P=1.000$), meningitis ($P=1.000$), PDA ($P=0.529$) and any stage of IVH ($P=0.516$) were not associated with severe ROP in this study. Complete data on the univariate analysis are displayed in Table 2.

After logistic regression, the infant's weight measured at completion of sixth week of life [$P=0.018$; odds ratio (OR): 0.997; 95% confidence interval (CI): 0.994–0.999] and number of days in mechanical ventilation ($P=0.002$; OR: 1.053; 95% CI: 1.019–1.088) were associated with severe ROP [Table 3].

Discussion

In our study, we included all preterm babies born with weight \leq 1000 g (range 505–1000 g) who survived from the initial ophthalmological examination to the completion of 42nd week of PCA. Our option for this approach was because BW is an easily recordable data, while GA is usually an estimated data, especially in the South American context. The GA among our patients ranged from 24 to 32 weeks at birth, with mean of 28.1 ± 2.0 weeks.

We reported an incidence of severe ROP of 12.7% and, interestingly, we did not identify any baby with severe ROP in zone I or with AP-ROP in our cohort. This aspect is unusual for cohorts of ELBW preterm

babies from the USA, Canada or even from European countries because usually this population has high incidence of zone I disease [7, 8, 21, 22]. Probably the high occurrence of zone I disease in that population is related to the more immaturity of those patients, usually around GA 25–27 weeks (or BW $<$ 700 g) in contrast with our cohort of ELBW with mean GA 28.3 ± 2.0 weeks and with mean BW of 844.04 ± 116.03 g. A study from Malaysia, published in 2009, identified 32.9% of ROP needing laser treatment and observed that zone I ROP occurred only in infants weighting \leq 751 g in a cohort of ELBW with similarity in BW and GA like the patients of our study [23]. A Canadian study, published in 2012, related that the overall incidence of stage 3 or worse ROP among extremely premature infants was 17.3% (36 of 207 ELBW) [7].

The main risk factors for severe ROP in our study were GA at birth ($P=0.029$), patient's weight at sixth week of life ($P < 0.001$) and number of days of oxygen therapy under mechanical ventilation ($P < 0.001$). This is in agreement with the knowledge about the pathogenesis of ROP that immaturity and oxygen therapy are fundamental keys in ROP development [24, 25]. In our cohort, babies that developed severe ROP stayed a mean of 50 ± 17 days in oxygen therapy under mechanical ventilation, while babies in the no-ROP/mild ROP group stayed a mean of 25 ± 21 days in the same condition ($P < 0.001$).

The postnatal low weight gain is recently recognized as an important predictor for severe ROP among low or among ELBW preterm infants [26–28]. We have observed this occurrence in our study although BW did not achieve statistical significance for severe ROP (mean BW 849.2 ± 115.6 g for no-ROP vs. 808.7 ± 115.5 g for severe ROP). The patient's weight measured at completion of sixth week of life showed significance (mean 1376.6 ± 275.4 g for no-ROP vs. 1120 ± 189.1 g for severe ROP; $P < 0.001$), suggesting that babies with severe ROP gained less weight in this period of life when compared with the babies that did not develop severe ROP. Reasons to explain these findings drive attention to the high frequency of clinical morbidities in this group. Among the 20 babies with severe ROP, 15 patients (75%) used erythropoietin to minimize need for blood transfusions, 13 patients (65%) received surfactant to alleviate respiratory distress syndrome, 8 patients (40%) received indomethacin to treat PDA and 14 patients (70%) developed clinical sepsis. This possibly means that babies that developed severe ROP are predominantly sicker babies with more difficulties to gain weight during this period when compared with patients with no-ROP/mild ROP group.

ROP is a preventable blindness disease. If not diagnosed and treated on time it can result in severe visual impairment or even blindness, affecting the normal motor, language, conceptual and social

TABLE 2
Univariate analysis of the recorded risk factors for severe ROP

Variables	No-ROP/Mild ROP patients (n = 137)	Severe ROP patients (n = 20)	P
Birth weight ^a	849.2 ± 115.6	808.7 ± 115.5	0.146
Gestational age ^a	28.4 ± 1.9	27.4 ± 2.0	0.029
Weight at sixth week of life ^a	1376.6 ± 275.4	1120.0 ± 189.1	<0.001
Small for gestational age	65 (47.4%)	7 (35.0%)	0.422
Female gender	80 (58.8%)	12 (60.0%)	1.000
Gemelarity	28 (20.4%)	4 (20.0%)	1.000
Oxygen therapy in nasal CPAP	97 (84.3%)	17 (89.5%)	0.738
Oxygen therapy in mechanical ventilation	75 (64.1%)	16 (80.0%)	0.256
Days in mechanical ventilation ^a	25.4 ± 21.6	49.9 ± 17.2	<0.001
Use of Indomethacine	50 (43.1%)	8 (42.1%)	1.000
Use of Surfactant	76 (64.4%)	13 (65.0%)	1.000
Use of Erythropoietin	73 (67.6%)	15 (83.3%)	0.285
Sepsis	85 (72.6%)	14 (73.7%)	1.000
Meningitis	6 (5.1%)	1 (5.3%)	1.000
Intraventricular hemorrhage	41 (29.9%)	8 (40.0%)	0.516
Persistent ductus arteriosus	21 (17.9%)	2 (10.5%)	0.529
Blood transfusions	105 (76.6%)	19 (95.0%)	0.077

nasal CPAP, nasal Continuous Positive Airway Pressure; ROP, retinopathy of prematurity.

^aData in mean ± standard deviation.

TABLE 3
Logistic regression

Variables	OR	95% CI	P
Gestational age	1.087	0.787–1.501	0.614
Weight at sixth week of life	0.997	0.994–0.999	0.018
Number of days in mechanical ventilation	1.053	1.019–1.088	0.002

OR, odds ratio; CI, confidence interval.

development of the affected child and having a high financial cost for the community [29]. In our patients, the mean PCA at diagnosis was 35.9 ± 1.8 weeks, while the mean PCA at treatment was 37.4 ± 1.8 weeks. In the study of Isaza and Arora, the mean PCA and chronologic age at first diagnosis of ROP were 33.6 weeks (range 30.7–38 weeks) and 58 days (range 26–103 days), respectively, and the mean PCA and chronologic age at type 1 ROP were 37.6 weeks (range 32.7–49.5 weeks) and 84 days (range 17–170 days), respectively [7]. These results are comparable with our findings. Hiraoka *et al.* investigated the incidence of ROP in 122 patients from 16 NICUs in Japan. The mean GA and BW were 26.7 weeks and 785.2 g, respectively. Authors concluded that in these ELBW preterm infants there was an increase in the survival rate as well in the incidence of severe ROP requiring treatment (41% of severe ROP). The median PCA at diagnosis was 32.5 weeks, and the

treatment was performed at the median of 35.6 weeks PCA [30].

There are limitations in our study: this was an institutional study conducted in an university and a level 3 NICU and included predominantly inborn patients or patients transferred in the first day of life to the institution, so the incidence of many described comorbidities and severity of ROP may not be representative of the Brazilian general population; the study was carried out during these past 10 years, and many practices of neonatal care may have improved worldwide, or even achieved local improvement such as better control over the oxygen use since birth, better ventilation techniques, widespread use of pulse oximetry avoiding fluctuations during oxygen therapy, improvements were also obtained in parenteral feeding for ELBW and routinely less use of vascular endothelial growth factor drugs, as erythropoietin, for example.

The incidence of severe ROP needing treatment among babies with BW < 1000 g at our institution was 12.5%. Patients were treated when ROP reached threshold disease at a mean PCA of 37.4 ± 1.8 weeks and around 1 week after diagnosis. Laser photocoagulation was effective to stabilize the natural progression of ROP among 19 treated patients. These results are in agreement with other published studies. No patient achieved ROP in zone I or AP-ROP in our cohort during the entire period of the study.

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