Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil

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Abstract

Aims To analyse the incidence and risk factors for retinopathy of prematurity (ROP) and survival rates among extremely low birth weight (ELBW) and very low birth weight (VLBW) preterm infants.

Methods A prospective cohort study of 352 infants admitted at a teaching hospital, Hospital de Clinicas de Porto Alegre, Brazil, between October 2002 and December 2006, was screened for ROP. The ELBW group comprised infants whose birth weight (BW) was ≤ 1000 g and the VLBW group comprised those infants whose BW were > 1000 g and ≤ 1500 g. Perinatal risk factors for ROP were assessed using univariate and multivariate analysis.

Results Of the 352 neonates screened, 88 were ELBW babies. Survival rates among ELBW and VLBW were 47.8 and 88.7%, respectively. ROP affected 48.9% of ELBW infants and 18.2% of VLBW babies. Threshold disease occurred in 21 patients, 15 of whom were born weighing < 1000 g. Only 2.3% of the neonates born with more than 1000 g developed treatable disease. Univariate analysis showed that gestational age (GA), BW, use of indomethacin and erythropoietin, blood transfusions, and intraventricular haemorrhage were associated with ROP. After logistic regression, the most important adjusted risk factors were BW (OR: 1.002; 95% CI: 1.001–1.003; $P = 0.003$), GA (OR: 1.254; 95% CI: 1.082–1.455; $P = 0.003$), and use of erythropoietin (OR: 2.486; 95% CI: 1.182–5.231; $P = 0.016$).

Conclusion This study showed reduced survival rates, high incidence of ROP, and a greater need of treatment among ELBW infants as compared to VLBW babies admitted in this institution.

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Keywords: prematurity; retinopathy of prematurity; extremely low birth weight; very low birth weight; risk factors; prevention of blindness

Introduction

The incidence of retinopathy of prematurity (ROP) has been the focus of extensive studies worldwide owing to the increasing survival rates now observed among premature infants. Although the incidence and severity of this condition have been decreasing in developed countries over the past two decades, these two factors are showing an increase in developing nations.¹ The most important groups of preterm babies developing this condition nowadays are very low birth weight (VLBW) preterm infants (birth weight (BW) > 1000 g and ≤ 1500 g) and extremely low birth weight (ELBW) preterm infants (BW ≤ 1000 g).²

The Brazilian guidelines for ROP screening were established by the Brazilian Ophthalmology Council, the Brazilian Paediatric Ophthalmology Society, and the Brazilian Society of Paediatrics after the first

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ROP Workshop, held in Rio de Janeiro in 2002. The joint statement issued at the time recommended ROP screening for all infants with BW ≤ 1500 g or gestational age (GA) ≤ 32 weeks or for any infant with BW > 1500 g, presenting with an unstable clinical course and designated as a high-risk case by the attending neonatologist. The incidence of blindness or severe visual impairment due to ROP in Brazil is estimated to be around 500–1500 cases/year.^{3,4}

Over the last years, epidemiological studies have shown falling mortality rates among ELBW infants in both developed and middle-income countries. The incidence of ROP and the need for laser treatment for this condition in the ELBW group were higher as well.^{5–7}

The aim of this study was to analyse the survival rates, possible risk factors, and the incidence of ROP among ELBW and VLBW preterm infants admitted in a teaching hospital in southern Brazil.

Materials and methods

This prospective cohort study included all preterm infants with BW ≤ 1500 g and/or GA ≤ 32 weeks admitted to *Hospital de Clínicas de Porto Alegre* (HCPA), a teaching and tertiary referral hospital, between October 2002 and December 2006. The incidence of ROP was analysed among ELBW (BW ≤ 1000 g) and VLBW infants (BW > 1000 g and ≤ 1500 g). Babies with BW > 1500 g and ≤ 32 weeks of GA examined during the screening for ROP (according to the Brazilian guidelines) were included in the VLBW group.

All patients were first examined in the sixth week of life and follow-up examinations were performed to investigate sequential retinal changes using the International Classification of ROP of 1984/1987.^{8,9} Neonates who died before the first ophthalmologic examination were excluded.

Pupils were dilated with tropicamide 0.5% and phenylephrine 2.5% eye drops, instilled 1 h before examination. Indirect ophthalmoscopy was performed using a 28 D lens (Nikon, Melville, NY, USA) and lid speculum (Alfonso Eye speculum, Storz, Bausch & Lomb Inc., CA, USA). All patients were first screened in the neonatal intensive care unit (NICU). After that, they were followed as outpatients until full vascularization of the retina had reached zone 3 or until full remission of ROP after treatment. All patients with stage 3 threshold ROP were treated with diode laser photocoagulation of the peripheral avascular retina under general anaesthesia or sedation. The worst stage of ROP was recorded. Ophthalmic examinations were always performed by the same ophthalmologist qualified for ROP screening (JBFF).

The main outcome studied was a diagnosis of any stage of ROP in the ELBW and VLBW groups. Perinatal variables considered for the study were BW, GA, gender, use of oxygen therapy and mechanical ventilation, single or multiple pregnancies, use of surfactant, indomethacin and erythropoietin therapy, sepsis, meningitis or intraventricular haemorrhage, and necessity of blood transfusions.

Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, USA). For the incidence of ROP, 95% confidence intervals (CI) were calculated. The χ^2 test was used to compare the clinical outcomes and odds ratio (OR) in both groups. Student's unpaired *t*-test was used to compare continuous data. A logistic regression model was performed and the adjusted OR (95% CI) was obtained for the risk factors included in the model. The study protocol was approved by the Ethics Committee of the HCPA (No. 03–247).

Results

From October 2002 to December 2006, there were 530 infants with BW ≤ 1500 g admitted to HCPA, of whom 380 survived until discharge (71.7%), and 353 babies out of that total were screened for ROP and enrolled in this study (92.6%).

Eighty-eight prematures fell into the ELBW group and 264 into the VLBW group. The mean BW among the ELBW group was 825.34 g (standard deviation (SD): 128.3) and 1329.05 g in the VLBW (SD: 191.5), $P < 0.001$. The mean GA among ELBW group was 28.5 weeks (SD: 2.1) and 30.9 weeks in the VLBW group (SD: 1.9), $P = 0.152$.

The survival rate in the ELBW group was 47.8% and in the VLBW group, it was 88.7% during the period covered by this study. The baseline characteristics of the study population are shown in Table 1.

The overall incidence of ROP and the incidence in each stage in both the groups are shown in Table 2. The incidence of ROP among ELBW babies was 48.9% (95% CI: 38.1–59.7%) and 18.2% (95% CI: 13.7–23.4%) for

Table 1 Baseline characteristics of the study population

	ELBW mean (SD)	VLBW mean (SD)	P-value
Number of patients	88	264	
Number of male gender (%)	39 (44.3%)	114 (43.2%)	0.179
Birth weight, g	825.34 (128.3)	1329.05 (191.5)	< 0.001
Gestational age, weeks	28.5 (2.1)	30.9 (1.9)	< 0.001

Abbreviations: ELBW, extremely low birth weight; VLBW, very low birth weight.

VLBW babies ($P < 0.001$). Threshold disease affected 17% of the infants in the ELBW group and 2.3% in the VLBW group ($P < 0.001$).

Table 3 lists the highest of the ROP stages found in each BW group. Fifteen babies whose BW was less than 1000 g displayed severe ROP (stage 3 or higher) and only six neonates whose BW was 1001 g or higher showed treatable ROP.

The need for treatment with diode laser in both groups is listed in Table 4. Fifteen out of 21 preterm babies with threshold disease fell into the ELBW group. The anatomic features showed complete regression of severe ROP in 19 treated patients, while one showed a progression of the disease to stage 4A of ROP, requiring scleral buckling. One patient dropped out of treatment after discharge and his condition progressed to stage 5 ROP.

Perinatal risk factors for ROP are summarized in Table 5. Univariate analysis indicates that GA, BW, the use of erythropoietin and indomethacin, blood transfusions, and intraventricular haemorrhage were associated with ROP in this cohort of 352 patients. After logistic regression, the most important adjusted risk factors in this cohort of patients were BW (OR: 1.002; 95% CI: 1.001–1.003; $P = 0.003$), GA (OR: 1.254; 95% CI: 1.082–1.455; $P = 0.003$), and use of erythropoietin (OR: 2.486; 95% CI: 1.182–5.231; $P = 0.016$).

Table 2 Incidence of ROP among ELBW and VLBW infants between 2002 and 2006

	ELBW	VLBW
Non-ROP	45 (51.1%)	216 (81.8%)
ROP*	43 (48.9%)	48 (18.2%)
ROP 1	12 (13.6%)	29 (11.0%)
ROP 2	16 (18.8%)	13 (5.0%)
ROP 3*	13 (14.8%)	6 (2.3%)
ROP 4*	1 (1.1%)	0 (0.0%)
ROP 5*	1 (1.1%)	0 (0.0%)
Total	88	264

Abbreviations: ELBW, extremely low birth weight; ROP, retinopathy of prematurity; ROP*, $P < 0.001$; ROP 3* and more; threshold ROP $P < 0.001$; VLBW, very low birth weight.

Table 3 ROP stages according to the birth weight for the whole cohort

Birth weight	Non-ROP	ROP 1	ROP 2	ROP 3	ROP 4	ROP 5	Total
≤500 g	0	0	0	0	0	0	0
501–750 g	10	2	8	5	0	1	26
751–1000 g	36	10	8	8	1	0	63
1001–1500 g	175	27	13	6	0	0	221
>1500 g	40	2	0	0	0	0	42
Total	261	41	29	19	1	1	352

Abbreviation: ROP, retinopathy of prematurity.

Discussion

The World Health Organization Vision 2020 programme has identified ROP as an important cause of blindness in countries with low infant mortality rates.¹⁰ Gilbert *et al* suggest that ROP is more prevalent in neonates born under 1000 g in industrialized countries. The disease is also emerging as a major cause of childhood blindness in middle-income countries like Brazil and in many other places in Latin America, Asia, and Eastern Europe, owing to the increasing survival rates among ELBW and VLBW prematures.^{5,10–12} Survival rates among preterm babies born with GA of 27–28 weeks have been reported to be as high as 90%, although the numbers vary widely across countries.¹³

Studies suggest that the incidence and severity of ROP show an inverse relationship with BW and GA,¹⁴ with few cases diagnosed in babies weighing over 1500 g or babies whose GA was >32 weeks at birth. Severe ROP has a higher incidence among infants born with GA <28 weeks or BW <1000 g. However, severe ROP is also reported in babies born at 34–35 weeks with BW 1500 g or more,¹⁵ especially when postnatal systemic complications occur, as shown in studies in India, China, and Lithuania.^{16–20}

HCPA is a level 3 hospital located in Porto Alegre, a city of 3 million inhabitants in southern Brazil. The hospital's NICU has 20 intensive-care beds. In the period covered by this study, the NICU received 530 babies with BW <1500 g, 380 of whom survived. Three hundred and fifty-two patients were screened for ROP following the Brazilian guidelines (92.6%).

Previous ROP studies at HCPA^{21,22} showed a prevalence of 28.5% in preterm infants with BW <1500 g or GA ≤32 weeks between 2002 and 2004. The present study showed an ROP incidence of 48.9% in ELBW babies. Survival rates among VLBW and ELBW patients at HCPA were 88.7 and 47.8%, respectively, during the period studied. In Brazil, Graziano *et al*²³ found a prevalence of 29.1% of any stage of ROP among 102 premature babies with BW <1500 g. That study drew attention to the high prevalence rates of ROP among babies with BW <1000 g (78.5%) and whose GA was <30 weeks (72.7%). Moraes *et al*²⁴ showed an ROP incidence of 90% in preterm babies whose BW was <1000 g. Although these important Brazilian unit-based studies date from the 1990s, the incidence of ROP found in our present study is considerably lower in spite of the higher survival rates of premature infants observed today.

A study in Tokyo, Japan, reported survival rates of 85.6% for preterm babies born in 2002 in a group whose mean GA was approximately 26.74 weeks and mean BW was approximately 782.25 g. Those authors²⁵ reported that 86.1% of those babies developed ROP and 41% of

Table 4 Treatable ROP among ELBW and VLBW groups and GA at pre-threshold ROP and at threshold ROP

	BW	GA	Gender	Group	ROP zone	GA at pre-threshold ROP	GA at treatment threshold ROP
	620	25	F	ELBW	II	34	36
	625	26	F	ELBW	II	34	36
	635	27	F	ELBW	II	35	36
	700	26	F	ELBW	II	35	36
	710	26	F	ELBW	II	35	36
	750	28	F	ELBW	II	37	38
	755	25	F	ELBW	II	35	36
	780	31	M	ELBW	II	37	40
	850	28	F	ELBW	II	36	37
	870	30	M	ELBW	II	38	40
	890	26	F	ELBW	II	35	37
	900	31	M	ELBW	II	38	40
	920	30	M	ELBW	II	36	38
	935	30	M	ELBW	II	36	37
	990	29	M	ELBW	II	38	39
	1055	27	M	VLBW	II	38	39
	1080	26	F	VLBW	II	35	37
	1230	31	M	VLBW	II	37	40
	1260	28	M	VLBW	II	36	37
	1315	32	M	VLBW	II	39	41
	1500	30	F	VLBW	II	39	40
Mean	928.4	27.9				36.3	37.9
Median	890	27				36	37
SD	243.8	2.4				1.6	1.7

Abbreviations: BW, birth weight; ELBW, extremely low birth weight; F, female gender; GA, gestational age; M, male gender; ROP, retinopathy of prematurity; SD, standard deviation; VLBW, very low birth weight.

Table 5 Perinatal risk factors for ROP for the whole cohort

Univariate analysis	ROP n = 91 (%)	Non-ROP n = 261 (%)	P-value
Male gender	57 (62.6)	142 (54.4)	0.18
Erythropoietin	79 (86.8)	199 (76.2)	0.03
Multiple gestation	16 (17.6)	38 (14.6)	0.50
Intraventricular haemorrhage	23 (25.3)	38 (14.6)	0.02
Oxygen in mechanical ventilation	54 (59.3)	126 (48.5)	0.09
Indomethacin	38 (41.8)	79 (30.3)	0.05
Surfactant	50 (54.9)	115 (44.1)	0.09
Sepsis	69 (75.8)	178 (68.2)	0.19
Meningitis	6 (6.6)	23 (8.8)	0.66
Blood transfusions	51 (56)	107 (41)	0.01
Birth weight ^a	1053.3 ± 281.4	1,253.4 ± 263.9	<0.001
Gestational age ^a	29.1 ± 2.3	30.7 ± 2.1	<0.001
Multivariate analysis	OR	95% CI	P-value
Birth weight	1.002	1.001–1.003	0.003
Gestational age	1.254	1.082–1.455	0.003
Erythropoietin	2.486	1.182–5.231	0.016
Intraventricular haemorrhage	1.884	0.991–3.581	0.053

Abbreviations: CI, confidence interval; OR, odds ratio; ROP, retinopathy of prematurity.

^aData showed in mean ± SD.

them were treated with laser, a much higher percentage of cases of treatable ROP. In that report, six patients (4.9%) showed retinal detachment. Both the survival rate and the incidence of ROP in the Japanese study were much higher than the values observed in Brazil.

In USA, Hussain *et al*²⁶ performed a retrospective assessment of 950 babies between the years 1989 and 1997 and found an incidence of ROP of 21.3%, of whom only 4.6% developed stage 3 disease or worse. In this group, none of the patients born with BW > 1000 g or GA

>28 weeks needed laser or surgical intervention. Another US study by O'Connor *et al*²⁷ identified an increase in the overall occurrence of threshold ROP from 2 to 5% between 1999 and 2000. Infants with BW <750 g were found to be at the highest risk for ROP. The findings from those studies in the USA are similar to those observed at HCPA, where 5.8% of all screened babies developed threshold disease. In our cohort, only six babies (2.3%) with BW >1000 g needed laser treatment while 17.0% of the ELBW group required treatment.

The screening guidelines for ROP adopted in Brazil after 2002 state that every newborn with BW ≤1500 g or GA ≤32 weeks should be screened. In the present study, 39 patients with BW >1505 g and 30 patients with GA >32 weeks were examined. None of these presented severe ROP or threshold disease. However, this should not be understood as a claim that current screening recommendations are too strict for Brazil. Although the incidence of treatable ROP in the VLBW group was lower (2.3%), the screening and treatment of those babies prevented disease progression in six patients (6/238) in the period covered by this study.

Recent studies suggest that ROP screening guidelines and the moment at which the first examination should be performed in ELBW patients are in need of revision, and advocate to start screening in the fourth week of life in these patients because all cases of threshold ROP were recorded before the 34th week of the infant's corrected age.^{28–30} In the HCPA study reported here, the mean GA for threshold disease was 37.9 weeks (SD:1.7) and the mean GA for pre-threshold diagnosis was 36.3 weeks (SD:1.6), considering the whole cohort of treated patients. Of the 21 patients who developed threshold disease at HCPA, there were 15 ELBW babies. Despite the higher incidence of threshold disease in the ELBW population, none of them developed severe posterior disease or zone 1 ROP.

Many papers analysed perinatal risk factors for ROP. Patz³¹ clearly demonstrated the causal effects of the administration of oxygen on the development of ROP. At HCPA, to accomplish tighter control of oxygen therapy, strict guidelines are applied. All neonate in critical condition is permanently controlled in his clinical aspects and by the use of pulse oximetry with a recommended saturation pressure between 88 and 94%. All NICU staff is regularly trained on the relationship between hyperoxemia and ROP. This training is helpful because it is possible to control and prevent the occurrence of severe ROP in most cases only by carefully monitoring hyperoxia and avoiding fluctuations.^{32,33}

In the present study, the main risk factors associated with ROP were low BW and low GA and the use of erythropoietin. The anaemia of prematurity is commonly

associated with low reticulocyte counts and deficient erythropoietin production. Since anaemia may decrease the amount of available oxygen to a critical level, preterm infants receive frequent blood transfusions.³⁴ There are studies confirming the role of blood transfusions on ROP in infants with BW of less than 1250 g.^{35,36} The use of recombinant human erythropoietin to reduce the need for blood transfusions in preterm infants has been suggested.^{37,38} Recently, cumulative recombinant erythropoietin exposure (as total 6-week dose) in infants born prematurely was associated with an increased risk for ROP. The non-hematopoietic properties of erythropoietin may account for these findings.³⁹ In our cohort of 352 premature babies, we found that 86.8% of the 91 patients with ROP and 76.2% of the 261 patients who do not develop ROP used the recombinant human erythropoietin ($P = 0.03$, Table 5).

The higher survival rate and the significantly higher incidence of severe ROP requiring treatment in ELBW preterm babies indicate that this group of patients should receive special attention by ophthalmologists and neonatologists when screening for the disease. The Brazilian guidelines for ROP screening adopted at HCPA after 2002 were shown to be effective in detecting all cases of threshold disease that needed laser treatment and this has helped to prevent blindness in 20 neonates since then. It is important to note that the present study is a unit-based approach and the observations herein cannot be applied to patients receiving care in a different setting.

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