

Incidence and risk factors of retinopathy of prematurity in the Lic. Adolfo López Mateos Regional Hospital, ISSSTE

Incidencia y factores de riesgo de retinopatía del prematuro en el Hospital Regional Lic. Adolfo López Mateos, ISSSTE

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Abstract

Objective: To determine the incidence of retinopathy of prematurity (ROP), and to analyze the main risk factors in premature newborns of the Hospital Lic. Adolfo López Mateos. **Methods:** We performed a prospective study with preterm infants with < 34 weeks of gestational age and a weight < 2000 g, during the period from September 2017 to July 2018. We analyzed risk factors such as gestational age, birth weight, treatment with oxygen, sepsis, blood transfusion, surfactant use, postnatal steroid use, respiratory distress syndrome, multiple pregnancy, bronchopulmonary dysplasia, patent ductus arteriosus, intra-ventricular hemorrhage, and apnea episodes. We analyzed continuous and categorical variables, performed a univariate logistic regression, and calculated a multivariate logistic regression model. **Results:** Ninety-one premature patients were studied from which 27 had ROP (29.6%). ROP incidence was greater in patients weighing < 1300 g or with a gestational age < 29 weeks. We found a significant risk association with sepsis (Odds ratio [OR] 8.48, 95% confident interval [CI] 3.07-23.44), gestational age ≤ 29 weeks (16.3, 95% CI 4.06-65.34), and birth weight < 1000 g (OR 11.25, 95% CI 2.89-43.8). **Conclusions:** This study demonstrates that the main risk factors for ROP are sepsis, gestational age, and birth weight. A gestational age < 29 weeks and a birth weight < 1000 g are particularly important. In a multivariate logistic regression model, sepsis and gestational age were the main factors associated with ROP. It is important to evaluate all newborns with a gestational age ≤ 34 weeks and/or weighing < 1750 g, with particular emphasis to smaller newborns.

Key words: Retinopathy of prematurity. Incidence. Risk factors.

Resumen

Objetivo: Determinar la incidencia de retinopatía del prematuro (ROP) y analizar los principales factores de riesgo en la población de recién nacidos prematuros del Hospital Lic. Adolfo López Mateos. **Método:** Se realizó un estudio prospectivo en el que se incluyeron prematuros con edad ≤ 34 semanas de gestación (SDG), con peso ≤ 2,000 g, durante el periodo

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de septiembre de 2017 a julio de 2018. Se analizaron factores de riesgo como edad gestacional, peso al nacer, oxigenoterapia, sepsis, transfusión sanguínea, uso de surfactante, uso de esteroide posnatal, síndrome de distrés respiratorio, gestación múltiple, displasia broncopulmonar, persistencia del conducto arterioso, hemorragia intraventricular, episodios de apnea. Se realizó un análisis estadístico para variables continuas y variables categóricas, regresión logística univariada y multivariada.

Resultados: Se estudiaron 91 pacientes prematuros, y se observaron 27 casos de ROP (29.6%). La incidencia de ROP fue mayor en pacientes que pesaban < 1,300 g o < 29 SDG. Se encontró asociación significativa de riesgo para sepsis (OR: 8.48; IC 95%: 3.07-23.44), SDG \leq 29 (OR: 16.3; IC 95%: 4.06-65.34) y peso al nacer < 1,000 g (OR: 11.25; IC 95%: 2.89-43.8).

Conclusiones: Este estudio demuestra que los principales factores de riesgo para el desarrollo de ROP son sepsis, edad gestacional y peso al nacimiento. La edad gestacional < 29 SDG y el peso al nacer < 1,000 g son particularmente importantes. En un modelo de regresión logística multivariada, la sepsis y el tiempo de gestación fueron los principales factores asociados al desarrollo de ROP. Es importante evaluar a todos los recién nacidos pretérmino de \leq 34 SDG y/o < 1,750 g de peso al nacimiento, y debe prestarse mayor atención a los más pequeños.

Palabras clave: Retinopatía del prematuro. Incidencia. Factores de riesgo.

Introduction

Retinopathy of prematurity (ROP) is a multifactorial retinal disease in which there is an interruption of normal vasculogenesis and formation of new blood vessels, which proliferate in a disorderly manner and cause neovascularization, vitreous hemorrhage and modification of the vitreous matrix with increased fibroblasts, which contract and cause retinal detachment¹.

This pathology is usually associated with premature birth, but the risk of its occurrence is a consequence of various interactive factors. Without a doubt, early gestational age (\leq 30 weeks of gestational age [WGA]) and low birth weight (\leq 1,500 g) are the most important risk factors in the development of ROP, but there are also other risk factors that cause a significant impact^{2,3}.

According to the World Health Organization, ROP is the second most frequent cause of blindness in children in Latin America⁴.

Overall, ROP remains the main threat to the vision of premature infants. In 2010, it was estimated that 184,700 premature babies developed any stage of ROP, 20,000 of whom were blind or severely visually impaired, and another 12,300 developed mild or moderate visual impairment⁵. Studies suggest that ROP is an increasingly important cause of avoidable blindness in China, Southeast and South Asia, Latin America and Eastern Europe⁶⁻⁸.

In the US, the incidence of ROP increased from 14.70% in 2000 to 19.88% in 2012, and the variables that best predicted ROP were female sex, birth weight and gestational age. The frequency of ROP was 2.40% in newborns of more than 2,500 g and 30.22% in newborns with a birth weight between 750 and 999 g⁹.

Although the real prevalence of ROP remains unknown, prior studies have been conducted in Mexico for the identification of ROP in our country. At the Centro Médico Nacional 20 de Noviembre, a prospective study was conducted to determine the prevalence of ROP between 1991 and 2004, in which 170 premature infants with a birth weight < 1,500 g and a gestational age of < 35 WGA were included. Forty-six infants were reported with stages I-III of ROP, with a prevalence of 10.61%, concluding that the incidence of ROP is inversely proportional to gestational age and birth weight¹⁰.

A study conducted at the Hospital Dr. Manuel Gea González of the Ministry of Health reported an incidence of 23%¹¹, and the Neonatology Service of the Hospital Infantil del Estado de Sonora reported an incidence of ROP of 58.1% in 2015². In 2012, the Department of Pediatrics of the Instituto Nacional de Perinatología reported 139 children examined in the Intensive Care Unit, 24.4% of whom were had ROP, 79% with stage I retinopathy, 18% with stage II and one with stage III. The zones involved were I, 12%; II, 79% and III, 9%. The associated risk factors were eclampsia, gestational age, multiple pregnancy, a longer hospital stay and mechanical ventilation, hypoxia, O₂ therapy, apnea, acidosis and hypercapnia¹².

The main risk factors for ROP are premature babies with a gestational age \leq 32 WGA, birth weight < 1,500 g, oxygen therapy with mechanical ventilation for more than 48 hours with a mechanical ventilator connected to an endotracheal cannula, nasopharyngeal ventilation or continuous positive airway pressure (CPAP). Other factors described are bronchopulmonary dysplasia, intraventricular hemorrhage, early sepsis, late sepsis, surfactant use, postnatal steroids, blood transfusion

and maternal risk factors, such as preeclampsia, eclampsia and diabetes^{4,12-14}.

According to the first ROP screening guidelines issued by the American Academy of Pediatrics, premature patients with a gestational age ≤ 32 weeks and a birth weight of less than 1,500 g are at risk of developing threshold retinopathy and retinal detachment and, therefore, irreversible visual damage¹³. The Ministry of Health in Mexico suggests screening the following population: a) all preterm infants with ≤ 34 WGA and/or $< 1,750$ g at birth, b) at the criteria of the attending physician, preterm infants > 34 WGA and a birth weight ≥ 1750 g who have received supplemental oxygen, and c) at the criteria of the attending physician, preterm infants with risk factors¹⁵; more attention should be given to smaller babies.

Premature newborns are at greater risk of developing neuromotor, sensory and cognitive development sequelae, as well as various visual complications such as refractive errors, amblyopia and strabismus. Therefore, early identification and timely treatment of premature babies at risk is essential to avoid the development of blindness¹².

Objective

The main objective of this work was to report the incidence and risk factors associated with ROP in the Hospital Regional Lic. Adolfo López Mateos, of the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado.

Methods

A prospective, descriptive study was conducted during the period from September 2017 to July 2018, at the Hospital Regional Lic. Adolfo López Mateos. The protocol was approved by the research and research ethics committees of the Hospital Regional Lic. Adolfo López Mateos (109.2018 Incidence of retinopathy of prematurity in a tertiary-care center in Mexico City). Premature babies with < 34 WGA and a birth weight $< 2,000$ g were analyzed, with the prior informed consent of the parents.

Exclusion criteria were patients whose severe systemic condition did not allow examination. Patients who were not brought to an outpatient appointment and those who died were also eliminated from the analyses.

Enrollment was carried out by fundus examination of premature patients, and they were divided based on

the presence or absence of ROP, and if present, by stratification. Risk factors such as gestational age, birth weight, oxygen therapy, sepsis, blood transfusion, surfactant use, postnatal steroid use, respiratory distress syndrome, multiple pregnancy, bronchopulmonary dysplasia, patent arterial duct, intraventricular hemorrhage, apnea episodes and maternal risk factors such as preeclampsia, gestational diabetes, HELLP syndrome (Hemolytic anemia, Elevated Liver enzymes, Low Platelet count), and eclampsia were analyzed.

Retinal examination was performed after application of ophthalmic drops with 50% diluted tropicamide and phenylephrine, one drop in each eye three times every 10 minutes. Topical anesthesia (tetracaine) was applied and assessed by indirect binocular ophthalmoscopy and a 28-diopter magnifying lens, using a pediatric blepharostat or desmarres lid retractors with indentation of the retinal periphery. At the end of the exploration, topical antibiotic drops (tobramycin) were applied. Patients were examined at 4 weeks after birth and the youngest ones when they were 31 weeks of corrected gestational age. Evaluations were carried out every 1 or 2 weeks in the neonatal intensive care unit or by outpatient consultation, depending on the patient's clinical condition, until the retinal vasculature was completed, and remission of retinopathy was observed.

The data were recorded on an electronic sheet using the Stata program, and statistical analysis was performed with the U-Mann-Whitney tests for continuous variables and Chi-square or Fisher test for categorical variables. Univariate logistic regression and a multivariate logistic regression model were also performed.

Results

This study included 91 premature infants with risk factors for ROP (182 eyes). Overall, 27 patients with ROP and 64 patients without ROP were identified, resulting in an incidence of ROP of 29.6%. In the group of patients without ROP a discrete male predominance was observed ($n = 34$, 53.1%), while among patients with ROP there was a discrete female predominance ($n = 15$, 55.6%).

When analyzing the different clinical variables, a significant presence of ROP was observed among patients with sepsis (70.4%). In addition to sepsis, gestational age and birth weight showed significant differences (Table 1).

In the group of patients with ROP, a higher frequency of patent arterial duct (37%), use of postnatal steroids (37%) and use of prolonged mechanical ventilation

Table 1. Clinical features

Parameter	All (n = 91)	Without ROP (n = 64)	ROP (n = 27)	p
Sepsis	33 (36.3)	14 (21.9)	19 (70.4)	< 0.001
Patent ductus arteriosus	20 (22.0)	10 (15.6)	10 (37.0)	0.024
Gestational diabetes	15 (16.5)	7 (10.9)	8 (29.6)	0.028
Multiple pregnancy	28 (30.8)	16 (25.0)	12 (44.4)	0.066
Prolonged mechanical ventilation	41 (45.1)	25 (39.1)	16 (59.3)	0.077
Female	45 (49.5)	30 (46.9)	15 (55.6)	0.449
Free-flow	47 (51.6)	31 (48.4)	16 (59.3)	0.224
Oxygen hood	47 (51.6)	32 (50.0)	15 (55.6)	0.535
Nasal cannula	42 (46.2)	27 (42.2)	15 (55.6)	0.191
CPAP	22 (24.2)	18 (28.1)	4 (14.8)	0.224
Premature membrane rupture	26 (28.6)	16 (25.0)	10 (37.0)	0.077
Preterm birth	36 (39.6)	25 (39.1)	11 (40.7)	0.246
Urinary tract infections	20 (22.0)	16 (25.0)	4 (14.8)	0.881
Placenta previa	4 (4.4)	4 (6.3)	0 (0.0)	0.355
HELLP syndrome	2 (2.2)	1 (1.6)	1 (3.7)	0.184
Cervicovaginal infections	18 (19.8)	13 (20.3)	5 (18.5)	0.525
Preeclampsia	36 (39.6)	26 (40.6)	10 (37.0)	0.844
Apnea episodes	13 (14.3)	9 (14.1)	4 (14.8)	0.749
Surfactant use	26 (28.9)	17 (26.9)	9 (33.3)	0.925
Postnatal steroids	23 (25.3)	13 (20.3)	10 (37.0)	0.441
Respiratory distress syndrome	37 (40.7)	23 (37.5)	13 (48.1)	0.063
Bronchopulmonary dysplasia	12 (13.2)	10 (15.6)	2 (7.4)	0.277
Gestational age (weeks)				
≤ 29	16 (15.6)	4 (6.25)	12 (44.4)	< 0.001
29.1-32	30 (33.0)	22 (34.4)	8 (29.6)	
32.1-34	45 (49.4)	38 (59.4)	7 (25.9)	
Birth weight (grams)				
≤ 1.000	13 (14.3)	4 (6.2)	9 (33.3)	< 0.001
1.001-1.300	18 (19.8)	10 (15.6)	8 (29.6)	
1.301-2.000	60 (65.9)	50 (78.1)	10 (37.0)	
Total additional O ₂ use (days)	10 (3-30)	8 (3-24.5)	26 (7-35)	0.007
Mechanical ventilation use (days)	0 (0-7)	0 (0-4)	5 (0-12)	0.029
Nasal cannula use (days)	0 (0-3)	0 (0-3)	2 (0-5)	0.054
Free-flow use (days)	1 (0-6)	0 (0-6)	2 (0-7)	0.423
Oxygen hood use (days)	1 (0-4)	0.5 (0-3)	2 (0-10)	0.119

CPAP: continuous positive airway pressure; HELLP: Hemolytic anemia, Elevated Liver enzyme, Low Platelet count; ROP: retinopathy of prematurity.

Table 2. Risk factors for the development of retinopathy of prematurity

Parameter	OR (95% CI)	p
Sepsis	8.48 (3.07-23.44)	< 0.001
Patent ductus arteriosus	3.18 (1.13-8.92)	0.028
Gestational diabetes	3.43 (1.10-10.71)	0.034
Gestational age (weeks)	0.67 (0.54-0.83)	< 0.001
≤ 29	16.3 (4.06-65.34)	< 0.001
29.1-32	1.97 (0.63-6.18)	0.243
32.1-34	1.0	-
Birth weight (grams)	0.99 (0.996-0.999)	< 0.001
≤ 1.000	11.25 (2.89-43.8)	< 0.001
1.001-1.300	4.0 (1.26-12.64)	0.018
1.301-2.000	1.0	-
Total additional O ₂ use (days)	1.04 (1.01-1.06)	0.009
Mechanical ventilation use (days)	1.06 (1.01-1.12)	0.014
Nasal cannula use (days)	1.11 (1.01-1.22)	0.033

Table 3. Risk assessment for retinopathy of prematurity

Model	z	OR (95% CI)	p
Sepsis	2.88	5.28 (1.70-16.37)	0.004
Gestational age (weeks)	-2.07	0.77 (0.61-0.99)	0.038
Birth weight (grams)	-1.50	0.99 (0.99-1.00)	0.134

(59.3%) were observed. Interestingly, only 4 patients needed antiangiogenic treatment.

Regarding risk factors related to pregnancy, in the ROP group, a higher frequency of gestational diabetes (29.6%) and multiple pregnancy was observed (Table 1).

A univariate logistic regression was performed to compare risk factors between patients with and without ROP. Similar to frequencies, sepsis was identified as the main risk factor associated with ROP (OR: 8.48; 95% CI: 3.07-23.44; $p < 0.001$) (Table 2).

Gestational age and birth weight also showed to be a high-risk factor for ROP development. Gestational age < 29 WGA was the main risk factor (OR: 16.3; 95% CI: 4.06-65.34; $p < 0.001$), followed by a birth weight < 1,000 g (OR: 11.25; 95% CI: 2.89-43.8; $p < 0.001$).

Multiple logistic regression analysis was used to assess the main risk factors for ROP development. The model that best explains the association is the one that is adjusted for sepsis, gestational age and birth weight (Table 3). This model confirmed that sepsis is the main risk factor associated with ROP development, followed

by gestational age, where the risk of developing ROP is 5.28 times higher in patients with sepsis and 0.77 times higher for every week of lower gestational age. Interestingly, birth weight does not contribute significantly to the risk in this model.

Discussion

In this study we determined the incidence of ROP and analyzed the main risk factors in the population of premature newborns of the Hospital Lic. Adolfo López Mateos. Premature babies with a weight ≤ 2,000 g and a gestational age ≤ 34 WGA were included, based on the recommendations of the ROP group and the Ministry of Health of Mexico¹⁵. Of the population analyzed in this study, 30 patients (30% of the total) had a birth weight > 1,750 g with less than 34 WGA. According to the criteria of the Ministry of Health and the ROP Group for patients with ROP, if the patient was exposed to oxygen, it is considered as a risk for ROP development, regardless of weight. Because 93% of our patients weighing > 1,750 g received supplemental oxygen, we decided to consider these patients at risk despite having a higher weight.

The incidence of ROP observed in this study was of 29.6%, which is similar to that reported in other countries, including 30.4% in Pakistan¹⁶, 29.5% in Iran¹⁷ or 29.2% in Singapore¹⁸, although higher than that reported in the US, which is of 10.45%¹⁹. This suggests that there is no greater genetic or environmental predisposition to develop ROP in our population, although there are factors associated with the level of development that reduce this risk.

The incidence of ROP was higher in patients who weighed < 1,300 g or were < 29 WGA. There was a significant risk correlation with sepsis (OR: 8.48; 95% CI: 3.07-23.44), WGA ≤ 29 (OR: 16.3; 95% CI: 4.06-65.34) and a birth weight < 1,000 g (OR: 11.25; 95% CI: 2.89-43.8).

In our population we identified a strong correlation with gestational age ($p < 0.001$) and birth weight ($p < 0.001$), similar to that reported worldwide. We also confirmed that the incidence of ROP is inversely proportional to gestational age and birth weight, that is, the lower the gestational age and the birth weight, the higher the incidence of ROP^{10,13,20-22}.

In addition, we observed a significant correlation of total supplemental oxygen use in patients with ROP, which was of 26 days ($p = 0.007$), supporting that oxygen use is a risk factor for ROP¹².

Gestational diabetes and patent arterial duct were previously reported as having a significant correlation with ROP, and we also found in our study a significant correlation ($p = 0.028$ and $p = 0.024$, respectively).

Regarding the use of mechanical ventilation, the oxygen input is high, despite using normal or low pressures, so prolonged use may be correlated with a high incidence of ROP. We also observed a statistically significant correlation ($p = 0.029$) despite the measures of regulation of these parameters in the neonatal intensive care unit^{2,4,12,14}.

Together, the parameters correlated with ROP development suggest that our population does not have a greater predisposition compared to that observed worldwide. Interestingly, of the 91 premature infants studied, only 4 needed antiangiogenic treatment; 2 of these premature babies had 9 risk factors (extremely low birth weight of 700 and 800 g, respectively), received oxygen for more than 45 days and mechanical ventilation for 30 days.

It has been reported that periods of apnea are the most significant risk factor for ROP development²³; however, in our study, we found no significant correlation. This could be explained by the association of apnea periods with acute pathological conditions, but not with chronic ones such as ROP²⁴, and a better oxygenation in premature infants with ROP in the neonatal intensive care unit.

The American Academy of Pediatrics has recommended the use of postnatal steroids only in newborns with extubation failure or prolonged mechanical ventilation; however, we did not observe an effect of these on the risk of developing ROP. This observation is consistent with several studies that does not report an effect of postnatal steroid use on ROP incidence^{15,25}.

This evidence seems to suggest that periods of apnea and steroid use are better managed in our intensive care unit, so they do not contribute to the development of ROP in our population.

Multiple studies have reported the role of neonatal sepsis in ROP development^{21,26}. In this study, sepsis was a risk factor with a significant correlation for ROP development ($p < 0.001$): it was observed in 57.6% of patients with ROP and was mainly associated with the development of ROP stages I (33.3%) and II (24.4%). This is explained by the secondary process mediated through cytokines and endotoxins that directly affects retinal angiogenesis. This process is frequently accompanied by hypotension, which may cause deterioration of tissue perfusion and retinal ischemia^{27,28}.

Premature newborns are particularly susceptible to infections, due to the low birth weight and gestational age. Exposure of the premature newborn to infections and inflammatory mediators, and the consequent development of early onset sepsis, is associated with an increased risk of developing ROP^{21,26}, mainly in patients with an extremely low gestational age. In this study we found a significant correlation ($p < 0.001$) of sepsis with the risk of developing ROP, with a relatively high incidence (57.6%). However, it is possible that in stage III there is also a strong correlation that we could not detect because they were premature patients whose severe systemic conditions did not allow examination.

In summary, at the Hospital Regional Lic. Adolfo López Mateos, we found that gestational age and birth weight contributed significantly to ROP development. We observed a strong correlation of sepsis with ROP development, so this risk factor must be evaluated and treated with special attention, since it is modifiable.

Although the trend is not similar in all units, surveillance and screening programs currently allow early detection, which has been reflected as a lower incidence of advanced stages of the disease. The decrease in the incidence of advanced ROP reflects a greater knowledge about risk factors and their timely management, as well as the improvement of neonatal care in our unit.

Conclusions

This study demonstrates that the main risk factors for ROP development are sepsis, gestational age and birth weight. From this factors, gestational age < 29 WGA and birth weight $< 1,000$ g had the highest correlation with the risk of developing ROP.

The multivariate logistic regression analysis model shows that sepsis is the main factor associated with ROP development, followed by gestational age. Interestingly, birth weight does not contribute significantly to the risk in this model.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical

research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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