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ORIGINAL ARTICLES

Retinopathy of prematurity: Eight-year outcomes of a Portuguese neonatal intensive care unit

Retinopatia da prematuridade: Resultados de 8 anos de uma unidade de cuidados intensivos neonatais portuguesa

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ABSTRACT

Introduction: Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina in preterm newborns and is an important and preventable cause of visual impairment in children. The aim of this study was to investigate the incidence of ROP in a sample of preterm infants with ophthalmologic observation criteria and its association with specific major risk factors.

Methods: Retrospective study of clinical records of premature infants with criteria for ROP screening in a Portuguese neonatal intensive care unit between January 2011 and December 2018.

Results: Three hundred thirty-five infants met the criteria for ROP screening. The incidence of ROP and severe ROP requiring treatment was 9.0% and 1.8%, respectively. No infants with gestational age (GA) > 30 weeks or birth weight (BW) > 1500 g developed ROP. Neonatal comorbidities such as respiratory distress syndrome and intraventricular hemorrhage were not significantly associated with the development of ROP. GA, BW, supplemental oxygen therapy, and surfactant administration were independent predictors for the development of ROP.

Discussion: Compared to neighboring countries with similar human development indexes, the incidence of ROP found in this study was relatively low. Implementation of the American Academy of Pediatrics/American Academy of Ophthalmology (AAO/AAP) guidelines in daily practice would potentially reduce the number of infants screened and allow diagnosis of most ROP cases.

Conclusion: Statistically significant risk factors should be considered when evaluating preterm infants. Modification of current screening guidelines may be useful and cost-effective, and result in less stressful experiences for infants undergoing unnecessary ophthalmologic examinations.

Keywords: intensive care unit; neonatal; Portugal; retinopathy of prematurity; risk factor; screening

RESUMO

Introdução: A retinopatia da prematuridade (ROP) é uma doença vasoproliferativa que ocorre na retina do recém-nascido prematuro, sendo uma importante e prevenível causa de baixa acuidade visual na infância. O objetivo deste estudo foi investigar a incidência desta patologia numa amostra de RN prematuros com critérios para observação oftalmológica, bem como a sua associação a determinados fatores de risco.

Métodos: Estudo retrospetivo de rastreios realizados numa unidade de cuidados intensivos neonatais portuguesa a recém-nascidos com

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critérios para rastreio de ROP entre janeiro de 2011 e dezembro de 2018.

Resultados: Trezentos e trinta e cinco recém-nascidos apresentaram critérios para rastreio de ROP. A incidência de ROP e ROP grave foi 9,0% e 1,8%, respetivamente. Nenhum recém-nascido com idade gestacional > 30 semanas ou peso à nascença > 1500 g desenvolveu ROP. Certas comorbilidades, como síndrome de dificuldade respiratória ou hemorragia peri-intraventricular, foram significativamente associadas ao desenvolvimento desta patologia. A idade gestacional, peso à nascença, terapia com oxigénio suplementar e administração de surfactante foram preditores independentes do desenvolvimento de ROP.

Discussão: Comparativamente a países vizinhos com índices de desenvolvimento humano semelhantes, a incidência de ROP neste estudo foi relativamente baixa. A implementação das orientações da *American Academy of Pediatrics/American Academy of Ophtalmology* reduziria potencialmente o número de RN rastreados e não deixaria casos de ROP por diagnosticar.

Conclusão: É importante que o clínico tenha em conta os fatores de risco significativos para esta patologia quando aborda um recém-nascido prematuro. A alteração das atuais recomendações de rastreio poderia ser útil e custo-efetiva e poupar o recém-nascido a stress associado exames oftalmológicos desnecessários.

Palavras-chave: cuidados intensivos neonatais; fatores de risco; Portugal; rastreio; retinopatia da prematuridade

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder commonly diagnosed in premature infants with low birth weight (BW). ROP is a leading cause of severe visual impairment in childhood. Although it is a treatable condition, in more severe cases it can lead to traction retinal detachment and blindness.

Globally, an estimated 184,700 babies out of 14.9 million preterm infants were found to have ROP in 2010, regardless of staging.[1] Nearly 32,300 infants worldwide become blind each year due to ROP.[1] Both the incidence and severity of ROP increase with decreasing gestational age (GA) and BW.[2,3] In middle-income countries, ROP is more common in babies with higher GA and BW compared to high-income countries, likely due to suboptimal care.[3-6]

Comparison of the incidence of ROP reported in population-based studies is challenging due to substantial variability in study design, GA of infants enrolled, survival rates, and treatment plans and strategies.

ROP usually presents in two phases. Phase one starts at preterm birth and lasts for the first few days of the newborn's life. During this phase, hyperoxia revokes the production of growth factors (GF) such as vascular endothelial growth factor (VEGF) and erythropoietin. The absence of GF delays normal retinal vascular development, which promotes retinal hypoxia. Phase two occurs weeks to months after birth (around 30 weeks postmenstrual age). At this time, the incompletely vascularized neural retina matures and its metabolic demands increase. The hypoxic avascular retina stimulates large increases in VEGF and erythropoietin, leading to uncontrolled retinal neovascularization in phase two, which can lead to retinal detachment and blindness without timely treatment.[7]

The most important risk factor for the development of ROP is prematurity. However, several risk factors have been identified. In multivariate analyses, low GA, low BW, prolonged assisted ventilation, duration of oxygen exposure, surfactant therapy, high blood transfusion volume, and cumulative disease severity have been associated with higher rates of ROP.[8-12]

ROP examinations can cause significant morbidity in neonates, including decreased oxygen saturation, increased heart rate, and increased apnea events. In addition, unnecessary examinations may increase the medical costs of ROP screening.[13,14] Therefore, although ROP overscreening has been considered acceptable, mainly due to the devastating consequences of not diagnosing severe ROP, the development of optimized screening protocols with high sensitivity and specificity in different populations would be ideal. Understanding the risk factors for ROP is essential to this end.

The aim of this study was to evaluate the incidence of ROP and some associated risk factors in a Portuguese institution, with the aim of contributing to the optimization of current screening guidelines.

METHODS

This was a retrospective study conducted in a Portuguese level III neonatal intensive care unit (NICU) between January 2011 and December 2018, based on data collected from patients' clinical records. According to the national protocol, eye examinations were performed in all infants with BW less than 1500 g and/or GA less than 32 weeks, in infants with BW less than 2000 g receiving prolonged oxygen supplementation, and in those with GA greater than 32 weeks with unstable clinical course considered at high risk of developing ROP, such as infants with hypotension requiring inotropic support.

The initial examination was performed 4-6 weeks postnatally or at 31-32 weeks postmenstrual age, whichever occurred later.[15]

Findings were classified according to the Revisited International Classification of Retinopathy of Prematurity.[16] If ROP was identified,

the examinations were repeated at specific time intervals according to the severity of findings. Follow-up examinations were determined by the attending ophthalmologist based on the classification of retinal findings according to the international classification.

For data analysis purposes, the sample was divided into two groups: group 1 – infants without ROP; group 2 – infants with ROP. Patients' clinical records were analyzed, namely for relevant risk factors that could play a role in the development of ROP.

This study was approved by the ethics committee of the participating institution.

Identification of risk factors

Potential risk factors for ROP were categorized into demographic characteristics, neonatal characteristics, neonatal comorbidities, and therapeutic interventions as follows:

- Demographic characteristics: gender
- Neonatal characteristics: GA, BW, type of pregnancy (singleton or multiple gestation), type of delivery, 5-minute Apgar score
- Neonatal comorbidities: sepsis, patent ductus arteriosus, intraventricular hemorrhage, respiratory distress syndrome
- Therapeutic interventions: blood transfusion, surfactants, oxygen supplementation

Definitions

GA was derived from last maternal menstrual period (LMP) or ultrasound parameters when LMP was uncertain. Sepsis was diagnosed based on positive blood cultures. Patent ductus arteriosus was confirmed by two-dimensional echocardiography. Serial transfontanellar ultrasound was used to diagnose intraventricular hemorrhage. Respiratory distress syndrome was diagnosed based on clinical and radiologic findings.[17]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0, Armonk, NY: IBM Corp.). Descriptive statistical methods were used to describe the study sample. Demographic and neonatal characteristics were described using frequencies (expressed as percentages) and sample means, including standard deviations (SD). Univariate analysis was performed to compare risk factors between groups using the Chi-Square Test and considering $p<0.05$ for statistical significance. Multivariate performed was conducted to compare statistically significant risk factors.

RESULTS

A total of 335 infants met the criteria for ROP screening and were included in the study. ROP was diagnosed in 30 infants, and severe type 1 ROP requiring treatment was diagnosed in six infants, corresponding to an estimated incidence of ROP and severe ROP of 9.0% and 1.8%, respectively.

Demographic and neonatal characteristics

The gender distribution of the study sample was balanced, with 169 (50.4%) males and 166 (49.6%) females included. The mean (± SD) GA was 26.9 ± 1.8 weeks in infants diagnosed with ROP and 30.5 ± 1.8 weeks in infants without ROP. **Table 1** depicts the demographic and neonatal characteristics of the study population according to the presence or absence of ROP and their association with the development of ROP. The mean BW was 836.3 ± 169.3 g in infants with ROP versus 1,324.3 ± 327.9 g in infants without ROP. Infants with GA below 27 weeks (6.3%) had a higher incidence of the disease (67%) compared to those with GA of 27-32 weeks (7.5%). Accordingly, the incidence of ROP was inversely proportional to the GA ($p<0.001$), with all newborns with ROP having GA ≤ 30 weeks.

Table 1 - Demographic and neonatal characteristics of the study population and their association with the development of ROP

	No ROP (%) (n=305)	**ROP (%)** (n=30)	*p*-value
Gender			0.959
Male	154 (50.5%)	15 (50%)	
Female	151 (49.5%)	15 (50%)	
Gestational age			<0.001
>32 weeks	100 (32.8%)	0	
27-32 weeks	198 (64.9%)	16 (53.3%)	
<27 weeks	7 (2.3%)	14 (46.7%)	
Birth weight			<0.001
>1500 g	65 (21.3%)	0	
1000-1500 g	180 (59%)	3 (10%)	
<1000 g	60 (19.7%)	27 (90%)	
Apgar score (5th minute)			0.652
7-10	300 (98.4%)	29 (96.7%)	
4-6	4 (1.3%)	1 (3.3%)	
≤3	1 (0.3%)	0 (0%)	
Multiple gestations	90 (29.5%)	7 (23.3%)	0.434

g, gram; ROP, retinopathy of prematurity

Most infants diagnosed with ROP (90%) had a mean BW lower than 1000 g. Neither infants with GA greater than 30 weeks nor those with BW greater than 1500 g developed ROP. The differences in the development of ROP according to multiple versus single gestation (p=0.434) and low versus high Apgar score (p=0.652) were not statistically significant (**Table 1**).

Neonatal comorbidities

The development of sepsis and patent ductus arteriosus was not statistically different between infants with and without ROP (p=0.888 and p=0.731, respectively). However, respiratory distress syndrome (p=0.014) and intraventricular hemorrhage (p=0.003) were significantly associated with the development of the disease (**Table 2**).

Table 2 - Neonatal comorbidities of the study population

	No ROP % (n = 305)	**ROP %** (n = 30)	*p*-value
Neonatal sepsis	118 (38.7%)	12 (40%)	0.888
Patent *ductus arteriosus*	63 (20.7%)	7 (23.3%)	0.731
Respiratory distress syndrome	222 (72.8%)	28 (93.3%)	0.014
Intraventricular hemorrhage	17 (5.6%)	6 (20%)	0.003

ROP, retinopathy of prematurity

Neonatal therapeutic interventions

Twenty-two of 54 newborns receiving blood transfusions developed ROP. Conversely, eight of 30 newborns who developed ROP did not receive transfusions (p<0.001). No association was found between the number of blood transfusions and the development of ROP (p=0.803; odds ratio [OR] 1.090; 95% confidence interval [CI] 0.553-2.147). In addition, the incidence of ROP was statistically significant in infants receiving surfactants (19.7%, p<0.001).

Oxygen supplementation was significantly associated with the development of ROP (p<0.001). Multivariate analysis of statistically significant risk factors is shown in **Table 3**. Only GA (p=0.018; OR 0.584; 95% CI 0.374-0.912), BW (p=0.036; OR 0.996; 95% CI 0.992-1.000), supplemental oxygen therapy (p=0.01; OR 1.069; 95% CI 1.028-1.112), and surfactant administration (p=0.006; OR 3.045; 95% CI 1.370-6.771) were independent predictors for the development of ROP (**Table 4**).

Table 3 - Multivariate analysis of risk factors

Risk factor	**AOR**	**95% CI**	***p*-value**
Gestational age (weeks)	0.584	0.374-0.912	0.018*
Birth weight (grams)	0.996	0.992-1.000	0.036*
Multiple gestation	0.819	0.179-3.758	0.798
Apgar score	1.242	0.794-1.941	0.342
Neonatal sepsis	0.362	.0120-1.024	0.055
Respiratory distress syndrome	0.251	.0031-2.031	0.195
Intraventricular hemorrhage	1.463	.0292-7.328	0.643
Blood transfusion	0.090	.0553-2.147	0.803
Surfactant	3.045	1.370-6.771	0.006*
Supplemental oxygen therapy	1.069	1.028-1.112	0.001*

*significant at level p <0.05

AOR, adjusted odds ratio; CI, confidence interval

Table 4 - Neonatal therapeutic interventions in the study population

	No ROP % (n = 305)	**ROP %** (n = 30)	*p*-value
Blood transfusion	32 (10.5%)	22 (73.3%)	< 0.001
Surfactant	9 (3.0%)	15 (50%)	<0.001
Supplemental oxygen therapy	43 (14.1%)	28 (93.3%)	<0.001

ROP, retinopathy of prematurity

DISCUSSION

The incidence of ROP varies widely among infant subgroups, reflecting differences in screening criteria, neonatal care, and population characteristics.

In the present study, the incidence of ROP and severe ROP was 9.0% and 1.8%, respectively. This is lower than reported in other studies. In Spain, an incidence of nearly 30% has been reported in preterm infants with GA ≤ 32 weeks or ≤ 1500g.[18,19] In France, a prospective analysis reported an incidence of ROP of 15% in infants with GA less than 31 weeks and/or BW less than 1500g.[20] In Portugal, some observational and retrospective studies have reported incidences of 15-42% in infants with GA ≤ 32 weeks or ≤ 1500g.[21-24] The type of hospital unit (level III), the broader criteria of the unit's protocol, and the characteristics of the study population – proper antenatal care and use of elevated rates of antenatal steroids; moderate representation of extreme prematurity in the sample; use of conservative ventilatory approaches by a specialized team and protocols aiming to avoid extreme fluctuations in oxygen saturation; individualized nutritional care adjusted to postnatal growth patterns – may partly justify the low incidence of ROP found. However, the fact that this study used retrospective data is a caveat that should be kept in mind when interpreting its results, as data were not directly obtained.

Studies have identified several putative risk factors for ROP.[8] In the present study, GA, BW, supplemental oxygen therapy, and surfactant use were found to be independent predictors for the development of ROP, which is consistent with the literature.[3,8,9,12,25] In addition, respiratory distress syndrome (p=0.014), intraventricular hemorrhage (p=0.003), and blood transfusions (p <0.001) were also significantly associated with the development of the disease.

The identification of at-risk preterm infants is important to establish screening criteria and to identify preterm infants who will develop severe ROP, thus avoiding unnecessary ophthalmologic examinations. Several studies have investigated the optimization of ROP screening by developing prediction models based on GA, BW, and weight gain, such as the WINROP model, the PINT-ROP model, the CHOP-ROP model, and the G-ROP model.[24-27] However, to date, no ROP prediction model has been used to exclude infants from screening or to reduce the number of examinations in low-risk infants. Near 100% sensitivity is required for models predicting the need for ROP treatment, as one missed case can result in lifelong blindness.[26]

The quality of neonatal care is a critical factor, and more older infants are at risk of developing severe ROP and require screening in areas where neonatal care is suboptimal. Worldwide inclusion criteria for ROP screening range from < 30 to 37 weeks GA and < 1000 to 2500 g BW.[27]

The latest ROP screening guidelines published by the American Academy of Pediatrics/American Academy of Ophthalmology (AAO/AAP) recommend that all infants with GA ≤ 30 weeks and/or BW ≤ 1500g or with unstable clinical course should be screened.[25]

In the present sample, no infants with GA >30 weeks or BW >1500g developed ROP. Based on this, the implementation of the AAO/AAP guidelines would result in a 25% reduction in the number of infants screened while potentially diagnosing all cases of ROP. The national screening consensus currently recommends the evaluation of all newborns with GA <32 weeks and/or BW <1500 g or with an unstable clinical course.[15]

Screening criteria and risk factors acknowledged in one country may not apply in another, where available perinatal care may not be comparable. Even within the same country, differences between level III and level IV NICUs may have also play a role in clinical outcomes. For these reasons, a multicenter study would be of great value in providing tools that could help improve the research and management of ROP in the future.

LIMITATIONS

The main limitation of this study is its retrospective nature. Relevant data were collected from medical records, which may contain documentation errors. The relatively small sample included may not be representative of the entire population studied. As a level III NICU, the study unit does not receive newborns undergoing major surgery or with congenital heart disease requiring cardiopulmonary bypass and/or extracorporeal membrane oxygenation, which may explain the low incidence of ROP found compared with other studies.

CONCLUSIONS

The present study found a low incidence of ROP compared to some neighboring countries with similar human development index. GA, BW, supplemental oxygen therapy, and surfactant administration were identified as independent risk factors for ROP, consistent with the literature. Based on these results, implementation of the AAO/AAP guidelines in clinical practice would predictably result in a 25% reduction in the number of infants screened while potentially diagnosing all cases of ROP. Modification of the current screening guidelines in Portugal could be useful and cost-effective, and spare infants from screening-related stress associated with unnecessary ophthalmologic examinations. However, as the level of neonatal care can vary considerably within countries and even within regions, it would be important to ensure that changes in screening criteria are based on data from as many NICUs, and not only from better performing units, to reduce the risk of bias. The authors hope that the results of this study will be useful for this purpose.

AUTHORSHIP

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