DOI: https://doi.org/10.2298/SARH240914088P
UDC: 617.735-053.32

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Examination of risk factors for the development of retinopathy in premature children

Jelica Pantelić[1,2], Igor Kovačević[1,2], Aleksandra Ilić[1,2], Snežana Polovina[3], Miroslav Stamenković[4,5], Jelena Vasilijević[1,2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Centre of Serbia, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Clinic for Endocrinology, Belgrade, Serbia;
[4]University of Belgrade, Faculty for Special Education and Rehabilitation, Belgrade, Serbia;
[5]Zvezdara University Medical Center, Clinic for Eye Diseases, Belgrade, Serbia;

SUMMARY

Introduction/Objective Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder in premature children's incompletely vascularized retina. Many factors slow down or prevent the normal development of retinal vascularization in premature babies. The aim of our study was to examine the risk factors in premature infants of gestational age (GA) of 25–36 weeks associated with the occurrence of severe ROP.

Methods The study was cross-sectional. The research included patients monitored by a screening program for ROP, i.e. prematurely born children with a body weight mass (BMW) ≤ 2000 g, and/or GA of ≤ 36 weeks.

Results Statistically significant differences were observed between the ROP and the control group in the mean values of GA, BWM at birth, Apgar score, and days of oxygen therapy. Also, frequencies of respiratory distress syndrome expression, broncho-pulmonary dysplasia, intraventricular hemorrhages, and requirement for mechanical ventilation were statistically significantly different between the two analyzed groups.

Conclusion Our work confirmed that low GA and low BWM are already accepted risk factors for ROP. The presence of perinatal asphyxia, the length of oxygen administration and assisted ventilation are significantly associated with the appearance of active forms of retinopathy. Sepsis and anemia were shown to be significantly associated with more severe forms of retinopathy, while hyperbilirubinemia was approximately present in both examined groups. More severe forms of intraventricular hemorrhages and necrotic enterocolitis are significantly more common in children with active retinopathy.

Keywords: retinopathy of prematurity; oxygen therapy; risk factors

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of the retina of prematurely born infants. It is a developmental vascular proliferative disorder in premature children's incompletely vascularized retina [1]. According to the International Classification for ROP (ICROP), the severity of the disease is described in five stages. Stage 1 is defined by the presence of the so-called demarcation line, stage 2 by the presence of the so-called ridge, and stage 3 by extraretinal fibrovascular proliferation. Stages 4 and 5 are severe conditions, the former characterized by sub-total retinal detachment and the latter by total retinal detachment [2]. The introduction of supplemental oxygen in the treatment of premature babies has been associated with the occurrence of more severe stages of this disease [1].

By introducing the monitoring of blood gas levels, it is possible to document and assess the need for oxygen better. Even with good oxygen monitoring, ROP persists, leading to examination of the influence of other factors involved in developing ROP and the possibility of other risk factors. A significant number of preterm infants require respiratory support and supplemental oxygen at birth [1, 3]. With the significant advances in neonatal care, the number of preterm infants with low gestational age (GA) and low body weight mass (BWM) has increased, resulting in a secondary epidemic of ROP [4].

Numerous factors slow down or prevent the normal development of retinal vascularization in premature babies. These are parameters of immaturity given at birth – gestational age and birth weight mass, as well as parameters of general health, treatment parameters and genetic factors [5, 6]. Dominant risk factors for the development of ROP are low GA (especially < 32 weeks), low BWM (< 1500 g, especially < 1250 g), sepsis, high concentrations of therapeutic oxygen, number of transfusions, damage to the central nervous system (CNS) [5, 6].

Therapeutic use of oxygen in the treatment of premature children is a significant risk factor for the occurrence of ROP, since high doses of oxygen lead to vasoobliteration of developing blood vessels. The transition to a room environment, which represents conditions of relative hypoxia, is accompanied by a vasoproliferative response and fibrosis [3, 7].

Other risk factors for the development of ROP are white race, heart disease, infections,

Received • Примљено: September 14, 2024
Revised • Ревизија: November 21, 2024
Accepted • Прихваћено: November 21, 2024
Online first: November 25, 2024

Correspondence to:
Jelena B. VASILIJEVIĆ
Clinic for Eye Diseases
University Clinical Centre of Serbia
Pasterova 2
11000 Belgrade, Serbia
bkjelena@gmail.com

multiple episodes of apnea, convulsions, respiratory distress, pneumonia, bradycardia, general health parameters (Apgar score – AS), intracranial bleeding, anemia, hyperbilirubinemia, and twin pregnancy [5, 8, 9]. Also, treatment parameters including the number of transfusions, use of surfactant, vitamin E, erythropoietin, and dexamethasone are important [5, 8, 9].

Current screening guidelines by the American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus state that all infants ≤ 30 weeks GA or ≤ 1500 g BWM should be screened for ROP, as well as larger infants based on clinical course [10]. In our country, screening covers prematurely born children with a BMW of 2000 grams or less, and a GA of 36 weeks or less.

Our study aimed to examine the risk factors in premature infants of GA of 25–36 weeks associated with severe retinopathy of prematurity. Our results are useful in recognizing risk factors and prognosis, thereby improving preventive and management strategies.

METHODS

The study was cross-sectional, from January 1, 2011, to December 31, 2015, at the Institute of Gynecology and Obstetrics of the University Clinical Center of Serbia in Belgrade. The research included patients monitored by a screening program for retinopathy of prematurity, i.e. prematurely born children with a BWM ≤ 2000 g, and GA of ≤ 36 weeks. Neonatologists select preterm children for ophthalmic screening based on risk factors. This study was undertaken according to the tenets of the Helsinki Declaration, is part of a doctoral dissertation that was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, record number 29/X-11.

The ophthalmological examination was performed in the intensive care units of the neonatology department. The examination was performed at the maximum wide pupil with an indirect binocular ophthalmoscope and a 20 D lens. An indentation was used to examine the peripheral parts of the retina. The ophthalmological examination determined the degree of ROP, based on which the premature children were divided into two groups. The classification of ROP was performed using the ICROP [2]. The first group consists of children without signs of retinopathy (normal findings) and children with forms of retinopathy that do not require therapy (ROPI and ROPII) – the control group, while the second group consists of children with an active form of the disease that requires therapy – the ROP group. The presence of risk factors was analyzed using medical records.

We examined post-natal risk factors: sex, GW, BWM at birth, mode of delivery (vaginal or cesarean section), children from multiple pregnancies, AS, intrauterine growth arrest, presence of anemia, hyperbilirubinemia, pneumonia, sepsis. We analyzed the need for oxygen therapy and mechanical ventilation (MV) as well as the presence of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). We also examined the presence of severe degrees (III and IV) of intraventricular hemorrhages (IVH) and necrotic enterocolitis (NEC).

Gas analyses and acid-base status were performed from a capillary blood sample from the heel, while blood count was performed from a capillary or venous blood sample. The criterion for anemia was a hemoglobin concentration of less than 90 mg/l. Ultrasound of the CNS was performed with a Logicum 3 Pro ultrasound device with a 7.5 MHz probe. Ultrasound findings of IVH are graded I–IV according to Papile [11]. Children with stages III and IV were included. The degree of RDS was assessed based on chest X-ray (grades I–V). The diagnosis of NEC was made according to Bell's classification [12]. Children who had stage I and II NEC and required medical treatment were included. Children with a more severe stage that required surgical treatment and transfer to another institution were excluded. Asphyxia was assessed based on the clinical picture, AS, and acid-base status, while sepsis was determined based on a positive blood culture, clinical picture, elevated C-reactive protein, leukocyte, platelet, and leukocyte formula values.

Statistics methods

The χ^2 test was used to test the significance of differences in nominal observational characteristics. Univariate and multivariate logistic regression analysis was used for association analysis. Multivariate modeling was done in two steps; in the first step, the Enter method was used. All predictors that were statistically significant in the univariate analysis were included in the analysis. Using the backward method with an entry criterion of $p = 0.05$ and an exclusion criterion of 0.01, predictors whose p-values in the model do not exceed 0.01 were obtained. Statistical analyses were performed using the SPSS statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA).

This study was conducted according to the guidelines of the Declaration of Helsinki, and is part of a doctoral dissertation, which was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, record number 29/X-11.

Informed consent was obtained from all parents whose children participating in the study after receiving a full explanation of the study.

RESULTS

Our study included 239 premature-born children, of which 123 (51.5%) were female and 116 (48.5%) were male. The ROP group contained 113 children, while the control group contained 126 children. In the ROP group, the frequency of diagnoses was as follows: ROP3+ 51 children (21.3%), AP ROP 36 children (15.1%), and ROP 2+2A 26 children (10.9%). In the control group, 70 children had normal findings (29.3%), 44 children (18.4%) had ROP I, and 12 children (5%) had ROP II. Not a single child had stages 4 and 5 of the disease. Children from the ROP group

Table 1. Clinical data of two premature infant groups

Clinical characteristics	ROP group n = 113	Control group n = 126	p-values
Sex M/F	58/55	58/68	0.413
GA Weeks	29.96 ± 1.93	31.42 ± 1.93	< 0.001*
BWM (grams)	1236.73 ± 236.37	1400.40 ± 298.03	< 0.001*
Caesarean section	64 (56.6%)	73 (57.9%)	0.839
Multiple pregnancies	39 (34.5%)	33 (26.2%)	0.308
AS	4.73 ± 1.7	6.22 ± 1.61	< 0.001*
PA	85 (75.2%)	51 (40.5%)	< 0.001*
Intrauterine growth arrest	36 (31.9%)	47 (37.3%)	0.378
Days of oxygen therapy	24.28 ± 17.3	13.45 ± 10.68	< 0.001*
MV	58 (51.3%)	30 (23.8%)	< 0.001*
RDS	94 (83.2%)	69 (54.8%)	< 0.001*
BPD	28 (25%)	11 (8.7%)	0.001*
Pneumonia	48 (42.5%)	29 (23%)	0.001*
Sepsis	46 (40.7%)	31 (24.6%)	0.008*
Anemia	101 (89.4%)	82 (65.1)	< 0.001*
Hyperbilirubinemia	47 (41.6%)	58 (46%)	0.490
ICH	21 (18.6%)	11 (8.7%)	0.026*
NEC	19 (16.8%)	6 (4.8%)	0.003*

ROP – retinopathy of prematurity; GA – gestational age; BWM – birth weight mass; PA – perinatal asphyxia; MV – mechanical ventilation; RDS – respiratory distress syndrome; BPD – broncho-pulmonary dysplasia; ICH – intracranial hemorrhage; NEC – necrotic enterocolitis; AS – Apgar score

Table 2. Presentation of the week of gestation and body weight of the two examined groups

Parameters		ROP		Control		Results
		N	%	N	%	
GA (weeks)	< 30	51	45.1	19	15.1	$\chi^2 = 28.862$ p < 0.001
	30–32	48	42.5	67	53.2	
	> 32	14	12.4	40	31.7	
BWM (grams)	< 1000	18	15.9	8	6.3	$\chi^2 = 15.190$ p < 0.001
	1000–1500	83	73.5	82	65.1	
	> 1500	12	10.6	36	28.6	

ROP – retinopathy of prematurity; GA – gestational age; BWM – birth weight mass

Table 3. Number of days on oxygen therapy and lung diseases

Parameters	Days on oxygen therapy							
	Mean		± SD	Perc. 25	Perc. 75	Min.	Max.	p-values
RDS	no	8.39	6.99	3.5	11.5	1	33	Z = -8.538 p < 0.001
	yes	23.32	15.62	11	32	2	103	
Pneumonia	no	16.09	14.82	5	22	1	103	Z = -4.736 p < 0.001
	yes	23.79	14.64	14	30	2	70	
BPD	no	14.36	10.15	6	19	1	44	Z = -8.312 p < 0.001
	yes	40.46	17.69	29	52	15	103	

ROP – retinopathy of prematurity; BPD – broncho-pulmonary dysplasia

were treated as follows: 99 children (87.6%) with vascular endothelial growth factor (VEGF) inhibitors, 10 children (8.8%) with laser photocoagulation, and seven children (35%) were treated with both treatments.

Table 1 shows clinical data recognized as clinical risk factors for severe ROP development. Statistically significant differences were observed between the ROP group and the control group in mean values of gestational age, BWM at birth, AS, and days of oxygen therapy. Also, frequencies of RDS expression, BPD, intracranial hemorrhage, and requirement for MV were statistically significantly different between two analyzed groups.

Table 2 shows the relationship between GW and BWM of both study groups. From the above table, it can be seen that the largest number of children who required therapy was < 30 weeks of gestation (51; 45.1%), and BWM 1000–1500 g (83; 73.5%). We observed that 14 children (12.4%)with > 32 weeks of gestation required treatment, as well as 12 children (10.6%) above 1500 g of BWM. On the other hand, 19 children (15.1%) of the control group born with < 30 GW did not develop an active form of retinopathy, nor did eight (6.3%) children with BWM < 1000 g.

The average number of days on oxygen for children in the ROP group was 24.28 ± 17.3 days, and for children in the control group 13.4 ± 10.68 days (Z = -5.555; p < 0.001). Children whose ophthalmological findings were normal were on average oxygen therapy for 8.01 ± 5.8 days, while children diagnosed with ROPI and ROPII were on average oxygen therapy for 20.25 ± 11.5 days. Children in the ROP group were on oxygen for an average of 24.28 ± 17.3 days. There is a statistically significant difference between the groups, namely the following: without ROP *vs.* ROP I/II (p < 0.001), without ROP *vs.* ROP (p < 0.001), and ROP I/II *vs.* ROP (p = 1.000).

The statistically significant differences were obtained in the length of oxygen use between children without lung disease and children with lung disease (p < 0.001), which is shown in Table 3. Children with BPD required the longest oxygen support (40.46 ± 17.69 days).

Our study showed that there is a close relationship between lung diseases (RDS, BPD, PA) and GA and BWM. RDS and PA occurs more often in children with lower GA (p < 0.001), while children with a lower BWM at birth were statistically more likely to have perinatal asphyxia (p < 0.001).

DISCUSSION

Retinopathy of premature children occurs because of the incomplete vasculogenesis of the retina at the time of the child's birth and exogenous factors of the external environment, the interaction of which can be a condition for the development of retinopathy. With premature birth, the child reaches conditions that are significantly different from intrauterine. [8]. Retinopathy of prematurity represents the most important field of cooperation between neonatologists and ophthalmologists.

The results of our study showed that low GA and low BWM are risk factors for the development of ROP. Retinal vascularization ends in 42 weeks GA. Premature birth severely disrupts vasculogenesis and changes the conditions

for its further development. Low BWM is a direct consequence of preterm birth [1, 4, 8].

The work of a group of authors shows similar results that prematurity is a dominant risk factor, which indicates that children born before 25 GA are twenty times more likely to develop severe retinopathy compared to children born after 28 GA [13].

In our study, the largest number of children with an active form of the disease was in the group of 1000–1500 g. The number of children with an active form of the disease decreases with increasing BWM (above 1500 g), which is expected. In our sample, 12 children with BWM > 1500 g developed forms of ROP that required therapy. Most guidelines limit the screening to children who were born with BWM ≤ 1500 g and GA ≤ 32 [9]. Our results showed that 14 children with GA > 32 required therapy. Using the recommended screening criteria [9], fourteen children with active disease would be missed, indicating that we still need to stick to broad screening criteria. Scientists from our country, indicating the need for wider regional screening [14], reached the same result. Current screening protocols in high-income nations effectively identify clinically significant diseases with high sensitivity, but cannot be generalized to other regions with different standards of neonatal care [8]. Other authors also draw attention to the risk of missing the active stage of the disease that requires therapy in children born with BWM > 1500 g and GA > 32 weeks [5]. The frequency of the disease that we obtained in groups below 1000 g is usually found in works coming from medium-developed countries [15]. This difference is the result of the application of advanced technology and science of high-income countries, resulting in better neonatal and health care. This results in a high survival rate for children with extremely low BWM. In medium-developed countries, the allocated funds are insufficient and without the possibility of providing a high level of neonatal care. As a result, we have less survival of children under 1000 g.

We monitored the number of days on oxygen and the use of MV in both groups. The average number of days on oxygen in the ROP group was significantly higher compared to the number of days on oxygen in the control group. In addition, MV is significantly more common in the ROP group compared to the control group. It is important to note that the average length of oxygen administration only in the control group of children with normal ophthalmological findings was significantly lower compared to children with forms of ROP that did not require treatment (ROPI and ROPII), while there was no statistically significant difference in the length of oxygen administration between the group of children diagnosed with ROPI/ROPII and ROP group. From this result, we can conclude that other risk factors are also important, because the children of the control group with initial forms of retinopathy (ROPI and ROPII) who regressed and did not require treatment spent a significant number of days on oxygen therapy, which did not statistically differ from the ROP group. Numerous works indicate that the number of days on oxygen therapy and the number of days on MV are considered risk factors for ROP [16, 17]. These colleagues indicate that prematurely born children or children with low BWM often require oxygen supplementation, where hyperoxic exposures at birth can lead to oxidative stress that can affect apoptosis and cell growth. The most difficult task of a neonatologist is to ensure adequate supplementation. The American Academy of Pediatrics suggests maintaining an optimal oxygen pressure of 50–80 mmHg, i.e. 6.7–10.7 kPa [9, 18]. Optimum oxygen pressure is not easy to achieve. Not only hyperoxia and the length of oxygen administration but also episodes of oxygen fluctuations can be serious risk factors for the development of retinopathy. Smaller fluctuations in oxygen saturation and gradual weaning from oxygen therapy are advised [19].

RDS, BPD, pneumonia, lung hemorrhages are conditions accompanied by apnea crises and the need for constant administration of oxygen, often with MV. Respiratory diseases are accompanied by gas exchange disorders and hypoxia. These conditions often require long-term care administration of oxygen, which carries an increased risk of hyperoxia. RDS is closely associated with preterm birth, with surfactant deficiency being the primary cause of RDS. The role of surfactant is to reduce the surface tension in the alveoli and prevent their collapse. In our sample, the frequency of RDS is high in both groups, although statistically significantly higher in the ROP group. Literature review found RDS requiring surfactant therapy to be an independent risk factor for ROP [8]. In our study, the presence of BPD was statistically significantly more frequent in the ROP group compared to the children who were not treated. Pneumonia also proved to be a significant risk factor in our research. Several studies reported a significant association between BPD and ROP [8, 19]. In our study, children with respiratory diseases were significantly longer on oxygen, were born earlier, and had a lower BWM at birth.

Anemia proved to be highly statistically significant as a risk factor in our sample. Some authors agree with our results [20], but in some, anemia did not affect the severity of ROP as an independent risk factor [21]. The role of hyperbilirubinemia as a risk factor is controversial. In our study, we did not determine that it is a risk factor for ROP, while some authors even indicate a protective effect of hyperbilirubinemia, due to its antioxidant effect. [22]. However, some authors have pointed out in their works that hyperbilirubinemia requiring phototherapy represents a surrogate for other risk factors for ROP [23].

ROP and IVH are serious complications in premature infants. The incidence of ROP and IVH has been shown to correlate inversely with GA and BWM. Immature and underdeveloped protection systems explain the vulnerability of the blood network of the CNS and the retina. Most papers show there is a significant difference in the frequency of IVH grade 3 or 4 in different categories depending on birth weight, together with advanced ROP stages compared to the control group [24], which is consistent with the results of our work. However, some authors did not find a significant relationship between IVH and ROP, explaining that with the improvement of neonatal care and the decrease in the frequency of severe IVH, there is a

weakening of the previously observed association between severe IVH and severe ROP [25].

NEC can increase the risk of occurrence of advanced forms of the disease. In our work, NEC occurred as a comorbidity significantly more often in the ROP group than in the control group. Reviewing the literature, the role of NEC in the progression of ROP to more severe stages require further investigation.

CONCLUSION

In conclusion, ROP is a complex disease with many risk factors, not all fully understood. Our work confirmed that low GA and BWM are already accepted risk factors for ROP. The method of delivery and multiple pregnancies did not affect the development of more severe forms of retinopathy. The presence of perinatal asphyxia, the length of oxygen administration, and assisted ventilation are significantly associated with the appearance of active forms of retinopathy, while there was no difference in the appearance of retinopathy between children with intrauterine arrest and children with appropriate BWM at birth. All investigated respiratory risk factors are directly related to the duration of oxygen therapy and the application of MV. Sepsis and anemia were shown to be significantly associated with more severe forms of retinopathy, while hyperbilirubinemia was approximately present in both examined groups. More severe forms of IVH and NEC are significant more common in children with active retinopathy. Our results also indicated the need for a wider screening protocol in our country and that the presence of additional risk factors during the development of the child points to the need for an earlier examination.

ACKNOWLEDGMENT

Presented results are a part of the doctoral dissertation: Pantelic J. Investigation of eNOS gene polymorphisms as a risk factor for the development of retinopathy of prematurity [dissertation]; Faculty of Medicine, University of Belgrade, Belgrade, Serbia, 2016.

Data availability statement: The datasets used and/or analyzed during the current study are available without restriction from the corresponding author. All relevant data are within the paper.

Conflicts of interest: None declared.

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Испитивање фактора ризика за развој ретинопатије код превремено рођене деце

Јелица Пантелић[1,2], Игор Ковачевић[1,2], Александра Илић[1,2], Снежана Половина[3], Мирослав Стаменковић[4,5], Јелена Василијевић[1,2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетски клинички центар Србије, Клиника за очне болести, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за ендокринологију, Београд, Србија;
[4]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[5]Клиничко-болнички центар „Звездара", Клиника за очне болести, Београд, Србија

САЖЕТАК

Увод/Циљ Ретинопатија недоношчади је развојни васкуларни пролиферативни поремећај у непотпуно васкуларизованој мрежњачи превремено рођене деце. Многи фактори успоравају или спречавају нормалан развој васкуларизације мрежњаче код превремено рођених беба.

Циљ истраживања био је да се испитају фактори ризика код недоношчади гестацијске старости 25–36 недеља повезани са појавом тешке ретинопатије недоношчади.

Методе Студија је спроведена као студија пресека. Истраживањем су обухваћени пацијенти праћени скрининг програмом на ретинопатију недоношчади, тј. превремено рођена деца са телесном масом ≤ 2000 *g*, и/или гестационом старошћу ≤ 36 недеља.

Резултати Уочене су статистички значајне разлике између ретинопатије недоношчади и контролне групе у средњим вредностима гестацијске старости, телесне масе при рођењу, Апгар скору и данима терапије кисеоником. Такође, учесталост експресије синдрома респираторног дистреса, бронхопулмоналне дисплазије, интравентрикуларног крварења и потребе за механичком вентилацијом статистички су се значајно разликовале између две анализиране групе.

Закључак Наш рад је потврдио да су ниска гестацијска старост и ниска телесна маса већ прихваћени фактори ризика за ретинопатију недоношчади. Присуство перинаталне асфиксије, дужина примене кисеоника и потпомогнута вентилација значајно су повезани са појавом активних облика ретинопатије. Показало се да су сепса и анемија значајно повезане са тежим облицима ретинопатије, док је хипербилирубинемија била приближно присутна у обе испитиване групе. Тежи облици интравентрикуларног крварења и некротични ентероколитис значајно су чешћи код деце са активном ретинопатијом.

Кључне речи: ретинопатија недоношчади; терапија кисеоником; фактори ризика