American Journal of Pediatrics
2022; 8(4): 213-217
http://www.sciencepublishinggroup.com/j/ajp
doi: 10.11648/j.ajp.20220804.14
ISSN: 2472-0887 (Print); ISSN: 2472-0909 (Online)

Risk Factor Associated with Retinopathy of Prematurity in Denpasar Tertiary Hospital

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To cite this article:

Dewa Ayu Angga Rainingsih, Made Sukmawati, I Made Kardana, I Wayan Dharma Artana, Putu Junara Putra, Putu Mas Vina Paramitha Cempaka. Risk Factor Associated with Retinopathy of Prematurity in Denpasar Tertiary Hospital. *American Journal of Pediatrics*. Vol. 8, No. 4, 2022, pp. 213-217. doi: 10.11648/j.ajp.20220804.14

Received: September 12, 2022; **Accepted**: October 8, 2022; **Published**: October 18, 2022

Abstract: *Introduction*: Retinopathy of prematurity (ROP) is an eye condition that affects the blood vessels of the retina in preterm infants. For the majority of children, retinopathy of prematurity occurs in a mild to moderate form and spontaneously regresses; however, more severe types of ROP can result in blindness in one or both eyes. Retinopathy of prematurity is often correlated with preterm delivery, however the risk for its emergence is a result of the interacting effects of other variables. This study seeks to identify the risk factors for ROP in neonates treated at the Prof. DR. I. G. N. G. Ngoerah Hospital in Denpasar, Bali. *Material and methods*: This study was retrospective study with design of case control study that conducted from Januari 2020 until January 2022. Samples of this study is neonates born prematurely undergone screening for ROP at Prof. DR. I. G. N. G. Ngoerah Hopital during study period. *Results*: The total sample of the study was 60 subjects, consisting of 30 subjects with ROP and 30 subjects without ROP. Multivariate analysis with logistic regression shows that gestational age < 32 weeks (OR 29.14; 95% CI 2.87 – 295.80), length of oxygen supplementation ≥ 14 days (OR 9.83; 95% CI 1.53 – 63.03), and severe infection (OR 12.17; 95% CI 1.05 – 141.69) was statistically significant for the occurrence of retinopathy of prematurity. *Conclusion*: The evaluation of risk factors that impacted the development of active ROP indicated statistically significant effects for gestational age, severe infection, and oxygen treatment duration. In order to avoid childhood blindness, timely screening and appropriate treatment are crucial.

Keywords: Retinopathy of Prematurity, Risk Factor, Neonate

1. Introduction

Retinopathy of prematurity (ROP) is an eye condition that affects the blood vessels of the retina in preterm infants. For the majority of children, retinopathy of prematurity occurs in a mild to moderate form, therefore the condition spontaneously regresses; however, more severe types of ROP can cause blindness in one or both eyes [1].

Improved obstetrical and neonatal care has enhanced the survival of very preterm (28-32 weeks gestation) and extremely preterm (below 28 weeks gestation) neonates, who may develop issues such as retinopathy of prematurity in the future (ROP). Globally, it was estimated that 184,700 out of 14.9 million preterm neonates (1.2% of the population) developed any stage of ROP, with a prevalence of 16% in the very and extremely preterm population. Twenty percent of newborns with ROP in high-income nations would ultimately require therapy [2].

The development of retinal vasculature begins approximately 16 weeks of gestation. It expands centrifugally from the optic nerve's head toward the periphery. Typically, complete vascular maturation of the retina occurs near term (40 weeks). Premature birth disrupts the development of the retinal blood vessels. Hyperoxia decreases retinal vascular endothelial growth factor expression in newborn preterm neonates (VEGF). Blood vessels constrict and can get destroyed, delaying the normal growth of retinal blood vessels. This hyperoxia-vasocessation causes avascular peripheral retina, which is clinically recognized as stage 0 or stage 1 of

retinopathy of prematurity. Early on, oxygen and nutrients can be transported to the retina by diffusion from the choroid, a rich circulatory bed underneath the retina. Eventually, the retina will outgrow its vascular supply, and the inner retina will require oxygen and nutrients from the retinal veins. Prolonged retinal hypoxia leads to an upregulation of VEGF, and the growth of abnormal/extraretinal vessels. Stage 2 ROP represents the first appearance of this abnormal growth, and it is seen clinically as a ridge at the border of the vascular-avascular retina. In addition to VEGF, this process is mediated by insulin like growth factor-1 (IGF-1) and other cytokines. Further growth of the abnormal vasculature tends to occur out of the plane of the retina and into the vitreous (stage 3 ROP). This is known clinically as neovascularization, because the vessels are largely incompetent, leaking proteins and other cytokines into the vitreous where they can precipitate localized contraction of the gel. This contraction can lead to traction and, eventually, elevation (detachment) of the retina (stages 4 and 5 ROP). "Plus disease" is the dilation and tortuosity of the normal retinal vessels in the posterior pole (most posterior part) of the retina [3-5].

Retinopathy of prematurity is often correlated with preterm delivery, however the risk for its emergence is a result of the interacting effects of other variables. Without a doubt, early gestational age (GA) below 31 weeks and low birth weight (BW) less than 1500g are the most significant risk factors for the development of ROP, but other factors, such as poor weight gain, reduced IGF increase, the percentage of oxygen in the inhaled air (originally considered not only a risk factor but also a direct causative factor for the ROP development), hypoxia, respiratory distress syndrome, twin pregnancy, a mother's history of hypertension, infection, etc. Due to severe visual impairment and the possibility of blindness, it is crucial to initiate ROP screening in premature infants at risk as soon as possible. According to the world's revised guidelines, a neonatologist should examine all infants born before 31 weeks of gestational age or weighing less than 1500 grams during the first 3 to 4 weeks after birth. Initial evaluation of premature babies with GA >31-32 weeks and BW >1500 grams should occur no later than 34 weeks. In addition, if there are clinical risk factors for the development of ROP, a neonatologist recommends ophthalmological evaluation in preterm infants of greater gestational age. Depending on the maturity of the retinal blood vessels, an ophthalmologist may advise further monitoring [4, 6].

Rarely studies investigated the risk factors for retinopathy of prematurity in Indonesia, particularly in Denpasar. In 2016, a research was undertaken at Prof. Dr. I. G. N. G. Ngoerah Hospital to assess the influence of time, fraction, and manner of providing oxygen on the occurrence of ROP in preterm newborns. That study indicated that the application of oxygen fractions greater than 40% resulted in an OR of 40,8 with a range of 2,8 to 594,8 (95% CI), P = 0.01. Other risk factors connected with ROP are also being researched. The purpose of this study is to evaluate the risk variables related with ROP in newborns in Prof. Dr. I. G. N. G. Ngoerah Hospital.

2. Materials and Method

This study was a retrospective study with a case control design to investigate the risk factors associated with ROP in the neonates at Prof Dr. I. G. N. G Ngoerah Hospital. This study was conducted during period of January 2020 until January 2022. The sample population in this study were neonates who born prematurely and undergone screening for retinopathy of prematurity treated at Prof Dr. I. G. N. G Ngoerah Hospital during study period.

Sampling was done by consecutive sampling. Sample size is measured using sample size formula for different proportion formula, two independent group. The minimum sample size in this study was 60 subjects. We collected data of ROP test result (with and without ROP), gender, birth weight (<1500 grams dan ≥1500 grams), gestational age (<32 weeks and ≥ 32 weeks), length of oxygen supplementation (≥ 14 days and < 14 days), asphyxia (APGAR score<7), and comorbid history (sepsis, meningitis, necrotizing enterocolitis, hyperbilirubinemia and hyaline membrane disease). The exclusion criteria in this study was if there were no complete data. If the subject meets the inclusion and exclusion criteria, the subject will be included in the study sample.

The collected data was then analyzed statistically using SPSS for Windows version 26.0. This research has received ethical approval from the Research Ethics Commission of the Faculty of Medicine, Udayana University/Prof. Dr. I. G. N. G. Ngoerah General Hospital with number 1203/UN14.2.2.VII.14/LT/2022.

3. Result

This research was conducted at Neonatology department at Prof. dr. I. G. N. G Ngoerah Hospital from January 2020 until January 2022. The total sample of the study was 60 subjects, consisting of 30 subjects with ROP and 30 subjects without ROP. The characteristic of subject with ROP mostly born by cesarian section (60%), very preterm infants (93.3%), female baby (53.3%), very low birth weight (86.7%), and asphyxia (73.3%). The mean for length of stay for ROP group was 48.37 (± 22.37) days. The characteristic of the subjects shown in Table 1.

Risk factors for gestational age, birth weight, asphyxia, gender, mode of delivery, comorbidities including NEC, meningitis, sepsis from positive culture result, hyperbilirubinemia, and HMD were analyzed using the chi-square test and presented with a large effect odds ratio (OR) with a 95% confidence interval (CI) as shown in Table 2. In this study, there was no effect on gender, mode of delivery, asphyxia neonatorum, meningitis, NEC, and hyperbilirubinemia. In the bivariate analysis, the risk factors that influence the occurrence of ROP were birth weight <1500 grams, (OR 4.97; 95% CI 1.38 – 17.81; p = 0.02), gestational age < 32 weeks (OR 16.0; 95% CI 3.21 – 79.55; p=0.01), length of oxygen supplementation ≥ 14 days (OR 15.54; 95% CI 3.81 – 63.35; p=0.01), positive culture result (OR 8.1; 95% CI 1.61 – 40.76; p=0.01), severe infection (OR 9.0; 95% CI 2.24 – 36.17; p=0.01), and HMD (OR 5.44; 95% CI 1.80 – 16.42; p=0.01).

Table 1. *Subject Characteristic.*

Characteristic	ROP (n = 30)	Control (n = 30)	Total (n = 60)
Mode of delivery			
Spontaneous (%)	12 (40)	11 (36.7)	23 (38.3)
Cesarian section (%)	18 (60)	19 (63.3)	37 (61.7)
Gestational age			
< 32 weeks (%)	28 (93.3)	14 (46.7)	42 (70)
≥ 32 weeks (%)	2 (6.7)	16 (53.3)	18 (30)
Gender			
Male (%)	14 (46.7)	16 (53.3)	30 (50)
Female (%)	16 (53.3)	14 (46.7)	30 (50)
Birth weight			
< 1500 grams (%)	26 (86.7)	17 (56.7)	43 (71.7)
≥ 1500 grams (%)	4 (13.3)	13 (43.3)	17 (28.3)
APGAR score			
asphyxia (%)	22 (73.3)	17 (56.7)	39 (65)
vigorous (%)	8 (26.7)	13 (43.3)	21 (35)
Comorbidities			
Sepsis (from positive culture) (%)	11 (36.7)	2 (6.7)	13 (21.7)
Meningitis (%)	7 (23.3)	3 (10)	10 (16.7)
NEC (%)	6 (20)	1 (3.3)	7 (11.7)
Hyperbilirubinemia (%)	12 (40)	14 (46.7)	26 (43.3)
Hyaline Membrane Disease (%)	21 (70)	9 (30)	30 (50)
Severe infection	15 (50)	3 (10)	18 (30)
Length of oxygen supplementation			
<14 days (%)	11 (36.7)	27 (90)	38 (63.3)
≥14 days (%)	19 (63.3)	3 (10)	22 (36.7)
Length of stay (mean ± SD)	48.37 (± 22.37)	28.27 (± 11.8)	33 (± 25)

Table 2. *Bivariate analysis for risk factor of ROP.*

Variable	ROP (n = 30)	Control (n = 30)	OR (95% CI)	P value
Spontaneous birth	12	11	1.15 (0.40 – 3.26)	1.00
Gender male	14	16	0.76 (0.27 – 2.11)	0.79
Gestational age < 32 weeks	28	14	16.0 (3.21 – 79.55)	0.01
Birth weight < 1500 grams	26	17	4.97 (1.38 – 17.81)	0.02
Born asphyxia	22	17	2.10 (0.71 – 6.22)	0.27
Comorbidities				
Sepsis	11	2	8.10 (1.61 – 40.76)	0.01
Meningitis	7	3	2.73 (0.63 – 11.82)	0.29
NEC	6	1	7.25 (0.81 – 64.45)	0.10
Hyperbilirubinemia	12	14	0.76 (0.27 – 2.12)	0.79
HMD	21	9	5.44 (1.80 – 16.42)	0.01
Severe infection	15	3	9.00 (2.23 – 36.17)	0.01
Length of oxygen supplementation ≥14 days	19	3	15.54 (3.81 – 63.35)	0.01

Multivariate analysis with logistic regression was performed on variables with p value <0.25 in bivariate analysis. The results of the analysis are shown in Table 3 which shows that gestational age < 32 weeks (OR 29.14; 95% CI 2.87 – 295.80), length of oxygen supplementation ≥ 14 days (OR 9.83; 95% CI 1.53 – 63.03), and severe infection (OR 12.17; 95% CI 1.05 – 141.69) was statistically significant for the occurrence of retinopathy of prematurity.

Table 3. *Multivariate analysis for risk factor of ROP.*

Variable	OR	95% CI	P value
Gestational age < 32 weeks	29.14	2.87 – 295.80	0.01
Severe infection	12.17	1.05 – 141.69	0.04
Length of oxygen supplementation ≥14 days	9.83	1.53 – 63.03	0.01

4. Discussion

In this retrospective analysis, we examined a total of 60 preterm newborns who were selected for ROP screening based on relevant criteria, including 30 neonates confirmed to have ROP and 30 neonates without ROP. The proportion of female respondents in the ROP group was 53.3%, greater than the proportion of male respondents (46%). Neonatal patients with ROP had a lengthier hospital stay (48.37 22.37 days) than those without ROP (28.27 11.8). In this investigation, gestational age 32 weeks was identified as a risk factor for ROP (OR = 29.14; 95% CI = 2.87 – 295.89; p = 0.01).

In their study, Yau et al. discovered that the incidence of

ROP increased with decreasing birthweight and gestational age below 32 weeks. For ROP screening at our institution (I. G. N. G. Ngoerah Hospital), the gestational age must be less than 34 weeks and the birthweight must be less than 1500 grams. Preterm newborns with additional risk factors and a gestational age of fewer than 37 weeks were included to provide a safety margin for patient selection, since there was still a chance that neonates might develop ROP necessitating treatment. Numerous studies revealed that the lower the BW and the GA, the greater the chance of developing ROP [7, 8]. Our logistic regression analysis confirmed these findings.

The frequency of ROP and its relationship with sepsis and infection are significant global concerns. This is the first study to our knowledge to investigate the risk of sepsis and infection in ROP. The findings of this study indicate that severe infection is one of the risk factors for developing ROP (OR = 12.17; 95% CI = 1.05 – 141.14; p = 0.04). According to a meta-analysis conducted by Wang et al., sepsis is associated with any stage of ROP (OR = 1.57, 95% CI 1.31 to 1.89) and severe stage of ROP (OR = 2.33, 95% CI 1.31 to 4.51) in preterm newborns. The microorganisms and their toxins cause sepsis-related damage in vascular endothelial cells, causing white blood cells to adhere readily to the blood vessel walls and form microthrombi in the small blood vessels of the retina; these microthrombi cause blood vessel obstruction and increased permeability. Eventually, a region of retinal non-perfusion develops, or an existing region grows. Sepsis frequently aggravates the body's oxidative stress response, and tiny dosages of oxidative stress products promote vascular endothelial cell proliferation and migration by transmitting signals to vascular endothelial cells via vascular endothelial growth factor-2. Inflammatory mediators and growth factors such as interleukin-1 can greatly boost the activity of hypoxia-inducible factor (HIF-1), whilst transforming growth factor- can block the degradation of HIF-1 via the signalling route. Finally, the HIF-l pathway induces and exacerbates ROP. In addition, other inflammatory agents, such as phospholipase-2 and prostaglandins, may influence retinal neovascularization [9, 10].

The role of oxygen therapy as a predictor of ROP has been reported in several other studies. In this present study, multivariate logistic regression analysis found that length of oxygen supplementation ≥14 days increasing risk for developing ROP (OR 9.83; 95%CI 1.53 – 63.03; p = 0.01). Das Kumar at el in their study found that neonates got oxygen up to 72 hours did not developed ROP. Those who received oxygen for duration of 170-218 hours and >218 hours developed ROP, with risk twice compared to neonates who received oxygen below 170 hours [11]. The formation of human retinal blood vessels often happens in a hypoxic environment during gestation. Current understanding of early postnatal retinal blood vessel development in premature infants is centered on the concept of physiologic hypoxia–driven, vascular endothelial growth factor (VEGF)–mediated angiogenesis [12, 13]. Preterm birth results in higher blood and tissue oxygen levels, which are further increased by oxygen supplementation. Reduced physiological hypoxia and delayed retinal vascularization. IGF1 facilitates VEGF signaling, and low serum IGF1 levels lead to delayed retinal vascularization: phase 1 of ROP development. This period of ROP development is the focus of clinical research of oxygen treatment initiated shortly after delivery and continuing for the first few weeks of postnatal life. Phase 2 of the development of ROP occurs when pathologic angiogenesis replaces normal angiogenesis. The peripheral avascular retina continues to expand, and the vitreous VEGF secretion rises. Simultaneously, IGF1 levels rise, enhancing the impact of VEGF on retinal angiogenesis. From the retina, abnormal blood vessels proliferate toward the high quantities of VEGF in the vitreous. The development of extraretinal vascular tissue is known as ROP stage 3. During phase 2 of ROP development, it has been hypothesized that increased oxygen supplementation may be beneficial: increased tissue oxygen may reduce VEGF levels and halt progression to severe ROP. Clinical trials of oxygen treatment conducted during this time, often after 32 weeks gestational age, may cause distinct effects on retinal blood vessel formation than those conducted earlier in the postnatal period [14, 15].

5. Conclusion

The analysis of risk factors that impacted the development of active ROP indicated statistically significant effects for gestational age, severe infection, and prolonged oxygen treatment duration. For the prevention of childhood blindness, timely screening and treatment are necessary. This study can be a basic study looking for risk factors for ROP. Further research can be done with a larger number of subjects and prospectively look at the degree and outcome for ROP in the presence of risk factors for ROP.

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