Risk Factors of Retinopathy of Prematurity in Tertiary Hospital

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Abstract

Introduction: Retinopathy of prematurity is a potentially blinding disease of the eye due to abnormal retinal vascularization. Gestational age, preterm birth, oxygen therapy, and RBC transfusion are some of the factors associated with ROP. **Purpose:** This study aims to determine the relation between gestational age, birth weight, duration of oxygen therapy, and RBC transfusion with ROP. **Methods:** This research is a case-control study using medical records data from Dr. Soetomo General Hospital in the period of January – June 2019. Data is analyzed using logistic regression analysis in SPSS v.25. **Results:** The case group consists of 22 patients with ROP while the control group consists of 66 patients without ROP. Gestational age (p=0.030; OR=3.10, 95% CI 1.113-8.606) and duration of oxygen therapy (p=0.012; OR=3.75, 95% CI 1.342-10.481) shows a statistically significant relation with ROP. There is no relation between birth weight (p=0.098; OR= 2.30, 95% CI 0.857-6.171) and RBC transfusion (p=0.881; OR=1.09; 95% CI 0.343-3.480) with ROP. **Conclusions:** There is a relation between gestational age and duration of oxygen therapy with ROP. Meanwhile, birth weight and RBC transfusion have no relation with ROP.

Keywords: Low birth weight; oxygen therapy; preterm birth; RBC transfusion; retinopathy of prematurity

1. Introduction

The eye acts as the organ of vision by collecting light and delivering information of what we see to the brain through the optic nerve. The information received is then transformed into a visual image. A visual impairment, which may occur early in life, may prevent the eye from serving its function. (1) It had been reported that preterm infants are susceptible to visual impairment. The risk of visual disturbances and blindness increase in preterm infants (gestational age < 37 weeks) compared to term-born infants. (2) Prior study reported that infants born with a gestational age of less than and including 25 weeks are at risk for blindness as a long-term poor outcome of extremely preterm birth. (1)

One of the leading causes of vision loss in children is retinopathy of prematurity. (3) Retinopathy of prematurity (ROP) is a disease of the eye characterized by abnormal vascularization. This may occur due to retinal tissue hyperoxia, thus causing down regulation of VEGF (vascular endothelial growth factor) and endothelial cell death. (4) The reduction of VEGF and IGF-1 (insulin-like growth factor 1) disrupts normal angiogenesis and retinal vascularization. (5)

Preterm infants born at < 31 weeks gestation and low birth weight infants (<1250 g) are frequently affected by ROP, according to the National Eye Institute. Every year, about 14.000-16.000 infants out of 3.9 million births in the United States suffers from retinopathy of prematurity. (3) One of the main contributors to vision loss that is related to ROP is South East Asia. (6) A Thailand based study reported that as much as 40.7% preterm infants have some degree of ROP. (7) Meanwhile, 30.3% infants in Cipto Mangunkusumo Hospital, Jakarta were reported to have retinopathy of prematurity. (8) However, ROP occurrence is not limited to South East Asian Countries. Hong reported a nationwide incidence of 29.8% in South Korea in a 12-year population-based study. (9) As much as 27% of infants in 69 NICUs in Turkey have some degree of ROP. (10) In Iran, the prevalence of retinopathy of prematurity was reported to be 23.5% in a meta-analysis. (11) Approximately 31.9% preterm infants with gestational age of < 31 weeks were reported to have retinopathy of prematurity, according to Holmström who conducted a study in Sweden. (12)

2. Method

This study is an analytical observational study with case-control design to analyze the relation between risk factors (gestational age, birth weight, duration of oxygen therapy, red blood cell transfusion) and retinopathy of prematurity. All low birth weight (< 2500 g) and preterm infants (< 37 weeks gestation) born in January 2019 – June 2019 in Dr. Soetomo General Hospital who underwent screening for ROP with complete medical records are eligible for the study. The variables collected includes sex, gestational age, birth weight, duration of oxygen therapy, red blood cell transfusion, method of birth, number of births, and existing complications.

Statistical analyses were performed using SPSS v.25. The data collected is analyzed using logistic regression test to determine the relation between risk factors and ROP with significance value of $p<0.05$. Odds ratio (OR) calculation is used to determine the size of association between the variables.

3. Results

Among 255 low birth weight and preterm infants born in January 2019 – June 2019 in Dr. Soetomo General Hospital, 28 infants were deceased, thus weren't screened for ROP, 110 infants did not undergo screening as they did not fit into the screening criteria, and 29 infants had incomplete medical records. Only 88 fulfil the inclusion and exclusion criteria, out of which 22 are patients with ROP and 66 are patients without ROP. Most of the ROP patients had stage 1 ROP, found in 11 patients (50%), 6 patients had stage 2 ROP (27.3%). Stage 3 ROP was found in 5 patients (22.7%), out of which, one patient presents with pre-plus disease, and another patient with stage 3 ROP presents with plus disease. The schematic distribution of the subjects is as shown in figure 1.
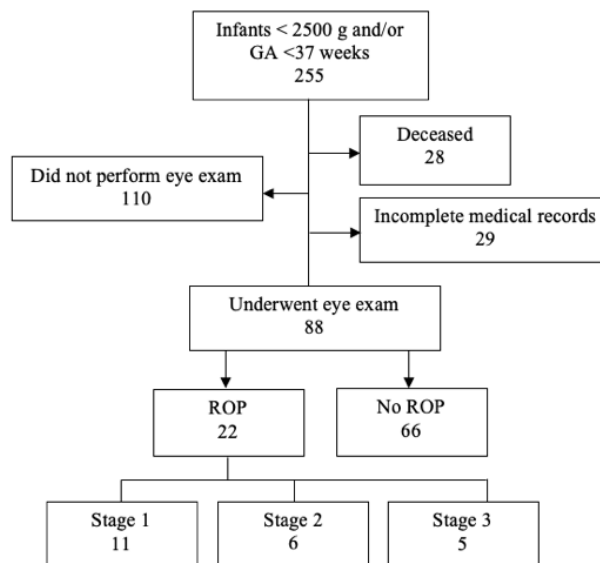

Fig 1. Schematic figure of the subject distribution

Table 1 shows that the subjects are dominated by female patients (59.1%), more than half of the subjects were born at > 32 weeks gestation (52.3%), born weighing ≥ 1500 g (64.8), received oxygen therapy for < 7 days (55.7%), born by caesarean section (75%), singleton (75%), and only 21.6% received RBC transfusion. Among ROP patients (case group), 68.2% were born at ≤ 32 weeks gestation, 50% were born weighing < 1500 g, 68.2% received oxygen therapy for ≥ 7 days, and 22.7% received RBC transfusion.

Table 1. Subject characteristics

Characteristics	ROP (n=22)	No ROP (n=66)	Total (n=88)
Sex, n (%)			
Female	14	38	52 (59.1)
Male	8	28	36 (40.9)
Gestational age, n (%)			
≤ 32 weeks	15	27	42 (47.7)
> 32 weeks	7	39	46 (52.3)
Birth weight, n (%)			
< 1500 g	11	20	31 (35.2)
≥ 1500 g	11	46	57 (64.8)
Duration of oxygen therapy, n (%)			
≥ 7 days	15	24	39 (44.3)
< 7 days	7	42	49 (55.7)
RBC transfusion, n (%)			
Yes	5	14	19 (21.6)
No	17	52	69 (78.4)
Method of birth, n (%)			
Spontaneous	1	20	21 (23.9)
Sectio caesarea	21	45	66 (75)
Forceps ekstraksi	0	1	1 (1.1)
Number of births, n (%)			
Single	17	49	66 (75)
Multiple	5	17	22 (25)

Multiple subjects in this study had multiple comorbidities. As seen on table 2, the most frequent comorbidity was neonatal jaundice found in half of the research subjects. Following that is congenital heart disease (CHD) including atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA). Eight subjects did not present with any comorbidity.

Among ROP patients, the most common comorbidity is neonatal jaundice in 12 subjects (54.5%). Followed by RDS in 8 subjects (36.4%), perinatal asphyxia, CHD and sepsis in 5 subjects (22.7%) respectively. Suspect sepsis and necrotizing enterocolitis (NEC) were found in 3 patients (13.6%) respectively, as well as pneumonia and anemia in 2 patients (9.1%) respectively.

Table 2. Present comorbidities among research subjects

Comorbidities	ROP (n=22)	No ROP (n=66)	Total (n=88)
Perinatal asphyxia, n (%)			
Yes	5	13	18 (20.5)
No	17	53	70 (79.5)

CHD, n (%)			
Yes	5	22	27 (30.7)
No	17	24	61 (69.3)
Neonatal jaundice, n (%)			
Yes	12	32	44 (50)
No	10	34	44 (50)
RDS, n (%)			
Yes	8	12	20 (22.7)
No	14	54	68 (77.3)
Suspect sepsis, n (%)			
Yes	3	6	9 (10.2)
No	19	60	79 (89.8)
Sepsis, n (%)			
Yes	5	10	15 (17)
No	17	56	73 (83)
Pneumonia, n (%)			
Yes	2	4	6 (6.8)
No	20	62	82 (93.2)
NEC, n (%)			
Yes	3	1	4 (4.5)
No	19	65	84 (95.5)
Anemia, n (%)			
Yes	2	7	9 (10.2)
No	20	59	79 (89.8)

Table 3 shows that gestational age of $\leq$ 32 weeks and oxygen therapy for $\geq$ 7 days are statistically significant with these results respectively, GA (p=0.030; OR= 3.10, 95% CI 1.113-8.606) and O2 therapy (p=0.012; OR= 3.75, 95% CI 1.342-10.481). Meanwhile, birth weight and red blood cell transfusion have a statistically insignificant relation with ROP (p>0.05). The analysis as shown in table 4 included only patients with ROP (case group). Results show that the relation between gestational age and duration of oxygen therapy is not statistically significant (p=0.448; OR= 2.06, 95% CI 0.313-13.574).

Table 3. Logistic regression analysis on risk factors of ROP

Risk Factors	ROP		Non ROP		*p value*	OR (CI 95%)
	n	%	n	%		
Gestational Age						
$\leq$ 32 weeks	15	35.7	27	64.3	0.030	3.10 (1.113-8.606)
> 32 weeks	7	15.2	39	84.8		
Birth Weight						
< 1500 g	11	35.5	20	64.5	0.098	2.30 (0.857-6.171)
$\geq$ 1500 g	11	19.3	46	80.7		
O2 Therapy						
$\geq$ 7 days	15	38.5	24	61.5	0.012	3.75 (1.342-10.481)
< 7 days	7	14.3	42	85.7		
RBC Transfusion						
Yes	5	26.3	14	73.7	0.881	1.09 (0.343-3.480)
No	17	24.6	52	75.4		

Table 4. Bivariate analysis on relation between gestational age and duration of O2 therapy among case group

Gestational Age	O2 ≥ 7 days		O2 < 7 days		*p value*	OR (CI 95%)
	n	**%**	**n**	**%**		
≤ 32 weeks	11	73.3	4	26.7	0.448	2.06 (0.313-13.574)
> 32 weeks	4	57.1	3	42.9		

4. Discussion

In this study, ROP patients are dominated by female similar to the findings of prior researches conducted in Indonesia (13,14), but in contrast with a research by Taliwongso *et al.* (15) In line with a previous study, frequency of ROP patients is higher among infants born at ≤ 32 weeks gestation. (16) On the contrary, Gaber *et al.* (17) reported higher frequency of ROP in older infants with gestational age (GA) of ≥ 32 weeks. The number of subjects with ROP are equally divided within the birth weight category with 11 subjects weighing < 1500 g and 11 subjects weighing ≥ 1500 g. Most of the patients with ROP were on oxygen therapy for ≥ 7 days, similar to the findings of a study conducted in Jakarta (18), but opposing to a report by Hakeem *et al.* (19) Out of 22 patients with ROP, only 5 received RBC transfusion. This result is in line with a study by Rao *et al.* (20) and opposite of a report by Hengartner *et al.* (21) Almost all of the patients with ROP were born by caesarean section and only one patient was born spontaneously. This result is in accordance with a research by Dewi *et al.* (22) Most of the case group subjects were born single, similar to the findings of previous studies (13,23) and in contrast with a study by Akkawi *et al.* (24)

Preterm birth is defined as a live birth before the gestational age reaches a full 37 weeks. (25) It is a condition affected by multiple factors, such as infection, history of preterm birth, premature preterm rupture of membranes, *et cetera*. (26) Although the cause often remains unidentified in cases of preterm labor. (25) Previous reports have linked increased ROP occurrence with younger gestational age. Lundgren *et al.* reported a significant decrease in the prevalence of infants needing treatment for ROP to only 0.1% among infants with 30-31 weeks GA. Meanwhile, the prevalence increased to 45.2% in the much younger 22-23 weeks GA infants. (27) Multiple studies have also reported lower mean gestational age in infants with ROP. (14,28,29)

Analysis on relation between gestational age and retinopathy of prematurity in this study shows a significant result with $p=0.030$. Infants with a gestational age of ≤ 32 weeks had 3.10 times greater odds (95% CI 1.113-8.606) to develop ROP compared to those born at > 32 weeks gestation. Similarly, a cohort study conducted a decade ago in Dr. Soetomo General Hospital Surabaya found significant results and reported gestational age of < 32 weeks as an independent risk factor for retinopathy of prematurity. (30) The result of this study is also in line with prior studies who reported GA ≤ 32 weeks as a significant risk factor for ROP. (13,17,31)

Low birth weight has long been associated as a risk factor for retinopathy of prematurity and is acknowledged as one of the most important risk factors for the development of ROP. However, it is closely associated with gestational age in premature infants. Therefore, it is still unknown which factor serves a larger contribution for the development of ROP as it is difficult to determine whether the prematurity precedes low birth weight or the other way around. (32)

A worldwide database which collects data from over 1000 NICUs estimated ROP incidence of 33.2% of all infants weighing < 1500 g at birth in 2010. (4) Over the years, numerous studies have reported higher ROP incidence or more severe ROP developing in lighter birth weights. (14,29,33,34) This indicates that the

incidence of ROP increases following the decrease in birth weight. Celebi *et al.* (29) reported a decrease in mean birth weight related to ROP status. Non-ROP infants have the highest mean birth weight, followed by ROP that does not require laser treatment, and laser treated ROP with the smallest mean birth weight. Binenbaum *et al.* (33) reported higher mean birth weight in patients with no severe ROP. Likewise, a study in a Tertiary Hospital in Surabaya reported greater mean birth weight in patients without ROP. (14)

This study did not find a significant relation between birth weight and ROP with $p=0.098$. Although odds ratio calculation does show that infants with BW of < 1500 g have 2.30 times greater chance (95% CI 0.857-6.171) for developing ROP compared to those born weighing $\geq$ 1500 g. This result is in accordance with a study conducted in Manado which reported insignificant relation between birth weight and ROP. (15) Contrary to the findings of this research, two previous studies in Saudi Arabia and Iran reported significant relation between birth weight and ROP ($p=0.04$, $p=0.007$). (35,36) Even as much as 11.60 times higher odds (95% CI 1.07-126.02) for the occurrence of ROP among infants weighing < 1500 g at birth in the Saudi Arabian based study. (35)

Premature infants are more prone than term infants to hypoxia. It is a condition in which the level of oxygen needed in tissues for normal organ function is not met. Hypoxia can result from a condition called hypoxemia where there is oxygen insufficiency in the blood. The normal oxygen saturation in infants during the first few hours of life is usually $\geq$ 88%. In an event where oxygen supply does not match the demand, oxygen supplementation is used to achieve the normal oxygen saturation level. (37)

In this research, the relation between duration of oxygen therapy and ROP appears to be significant with $p=0.012$. Retinopathy of prematurity is 3.75 times (95% CI 1.342-10.481) more likely to develop in infants who received oxygen therapy for $\geq$ 7 days compared to those who received supplementation for less than a week. This finding is in line with previous Indonesian reports conducted in two different cities. The Jakarta and Bali based studies found higher odds for the occurrence of ROP among infants who were on oxygen therapy for $\geq$ 7 days with these values respectively (OR=11.50; 95%CI 4.51-29.13, OR=11.0; 95% CI 3.20-37.20). (18,38) The mode of ventilation and oxygen fraction may also contribute to the development of retinopathy of prematurity. (38). Although Munadzilah *et al.* (39) concluded otherwise and reported insignificant difference between the use of lower oxygen fraction (21-30%) and 100% oxygen concentration towards retinopathy of prematurity outcome.

Decrease in hemoglobin (Hb) levels during the first few weeks of life is a physiologic occurrence in newborn. In term infants, the Hb value usually stays above 10 g/dL at age 10 to 12 weeks. (40) Strauss *et al.* (40) also observed that hemoglobin value in preterm infants with heavier birth weight is higher compared to those with lighter birth weight. Some organs or systems including the hematopoietic system may be underdeveloped in premature birth due to the shortened gestational age, thus resulting in anemia. Preterm infants typically undergo numerous laboratory testing that require phlebotomy which may contribute to blood loss. (41) RBC transfusion is given to preterm infants if deemed necessary with the goal of increasing oxygen transport to the organs. (42)

This study found non-significant relation between RBC transfusion and ROP with $p=0.881$. Infants who received RBC transfusion have 1.09 times (95% CI 0.343-3.480) higher odds for the occurrence of ROP compared to those who never received red blood cell transfusion. Badriah *et al.* (18) and Hengartner *et al.* (21) who previously conducted a study in Indonesia and Switzerland respectively reported similar findings where RBC transfusion is not related to the development of ROP ($p=0.327$, $p=0.179$). In contrast, two previous studies reported significant relation between red blood cell transfusion and retinopathy of prematurity. (28,35) Wu *et*

al. (28) who conducted a study in China reported 4.17 times greater odds for the occurrence of ROP in infants who received red blood cell transfusion.

Bivariate analysis using chi-square test found no relation between gestational age and duration of oxygen therapy (p>0.05). By odds ratio calculation in the analysis shown in table 3, duration of oxygen therapy possess greater risk for the development of ROP compared to gestational age. However, the need to use oxygen supplementation is also affected by younger gestational age itself. As infants who are born prematurely have yet to complete a full-term pregnancy, the respiratory organ and system are often not sufficient to support the respiratory needs of a premature infant. (43) Odds ratio calculation between gestational age and duration of oxygen therapy, as seen in table 4, shows that infants born at ≤ 32 weeks gestation are 2.06 times (95% CI 0.313-13.574) more likely to receive oxygen supplementation for ≥ 7 days. Duration of oxygen supplementation is adjusted to the infant's clinical condition. If SpO2 level stays > 90% and the infant does not present with alarming clinical signs, oxygen can be disconnected gradually. (37) For infants with CPAP ventilation, discontinuation of support is based on multiple factors, such as infant's weight, chronologic age, clinical condition, and breathing stability. (44)

5. Conclusion

In conclusion, the relation between gestational age and ROP, as well as between duration of oxygen therapy and ROP is statistically significant. However, there is no relation between birth weight and ROP, and RBC transfusion and ROP. Also, there is no relation between gestational age and duration of oxygen therapy among ROP patients. Using a larger sample with a longer period of research, as well as more variations in subject characteristics and risk factors are suggested.

Acknowledgements

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