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Original Article

Incidence and risk factors of retinopathy of prematurity

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Abstract

Background Retinopathy of prematurity (ROP) is one of the main causes of visual impairment in premature infants.

Objective To determine the incidence and risk factors for ROP in premature infants.

Methods This retrospective study included premature infants born in Stella Maris Women's and Children's Hospital and admitted to the neonatal intensive care unit (NICU) and Neonatology Department from November 2009 to May 2012. We included all premature infants with body weight (BW) < 1500 g or gestational age (GA) ≤ 32 weeks, and selected infants with BW 1500 - 2000 g or GA > 32 weeks with unstable clinical courses who had been screened for ROP. Data was analyzed with Fisher's exact test and independent t test.

Results Of the 48 premature infants in the study, ROP was detected in 6 (12.5%) of the subjects. Stages of ROP were classified according to the International Classification of Retinopathy of Prematurity. Stage 1 ROP was detected in 1 (2.1%) subject; stage 2 ROP was detected in 3 (6.25%) subjects; and stage 3 ROP was found in 2 (4.2%) subjects. The 2 infants with stage 3 ROP required surgery. No ROP was detected in infants with GA ≥ 30 weeks or BW > 1250 g. Respiratory distress syndrome (RDS), sepsis, blood transfusion, and apnea were found to be associated with development of ROP. Duration of oxygen therapy was found to be a significant risk factor for ROP in a comparison of the no ROP group to the ROP group: 14.0 (SD 9.508) days vs. 3.81 (SD 5.218) days, respectively ($P<0.05$). In addition, the duration of continuous positive airway pressure (CPAP) usage was also a significant risk factor for ROP, with 1.83 (SD 1.329) days in the ROP group vs. 0.76 (SD 1.122) days in the no ROP group ($P<0.05$).

Conclusions The incidence of ROP in the premature infants in our study is 12.5%. Retinopathy of prematurity is associated with lower BW, lower GA, lower Apgar score at the 5th minute, RDS, sepsis, apnea, blood transfusion, aminophylline usage, as well as longer duration of oxygen therapy and CPAP usages. **[Paediatr Indones. 2013;53:76-82.]**

Keywords: *retinopathy of prematurity, risk factor, incidence*

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature infants.[1] Recent advances in neonatal care have improved the survival rates for premature infants, but this has been accompanied by an increase in the incidence of ROP.[2-5] Retinopathy of prematurity is one of the main causes of visual impairment in premature infants and is the cause in 20% of blind preschool children in the United States.[6,7]

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Several risk factors have been associated with ROP including prematurity and the associated retinal immaturity at birth. Oxygenation, respiratory distress, apnea, bradycardia, heart diseases, infection, hypercarbia, acidosis, anemia, and the need for transfusion, are also thought to be contributory factors.[1,7]

In general, infants with lower gestational age (GA), lower birth weight (BW), or are more ill have increased risk for ROP. Extreme prematurity is known to be the most significant risk factor for ROP.[1,7] In 2006 the American Academy of Pediatrics (AAP) published new screening guidelines for ROP. Infants with BW < 1500 g or GA ≤ 32 weeks, and selected infants with a BW 1500 - 2000 g or GA > 32 weeks with an unstable clinical course, including those requiring cardiorespiratory support and those believed by their attending pediatrician or neonatologist to be at high risk, should have retinal screening examinations.[1] In our hospital, there has been no study on the incidence and risk factors of ROP. The objectives of this study were to determine the incidence and risk factors for ROP in premature infants.

Methods

This study was a retrospective observational analysis review of medical records of all premature infants who were born in and admitted to the NICU and Neonatology Department of Stella Maris Women's and Children's Hospital, Medan from November 2009 to May 2012, and who met the established criteria for ROP screening. We screened infants with BW < 1500 g or GA ≤ 32 weeks, and selected infants with a BW 1500 - 2000 g or GA > 32 weeks with an unstable clinical course. We excluded infants who failed to survive longer than 28 days for the first ROP screening, those born outside of Stella Maris Women's and Children's Hospital, and those who did not get eye examinations.

Forty-eight premature infants underwent eye examinations by ophthalmologists to detect ROP. The first examination was performed at 4 – 6 weeks of chronological age or 31 -33 weeks corrected age. Examinations took place in the NICU and Neonatology Department or at the outpatient facility (for discharged infants). Prior to examination, both pupils were dilated with topical eyedrops (2.5% efrisel and 0.5% tropicamide), alternately until full dilation occurred. During examination, topical anesthesia with 0.5% tetracain hydrochloride was applied to subjects' pupils. Indirect ophthalmoscopy was performed using a lid speculum and sclera indentation was done to examine the peripheral retina.

Stages of ROP were classified according to the International Classification of Retinopathy of Prematurity as follows:[8]

Stage 1. Demarcation line separating the avascular retina anteriorly from vascularised retina posteriorly with abnormal branching of small vessels immediately posterior to this
Stage 2. Retinal ridge: the demarcation line has increased in volume, but this proliferative tissue remains intraretinal
Stage 3. Ridge with extraretinal fibrovascular proliferation
Stage 4. Partial retinal detachment
Stage 5. Total retinal detachment

In subjects with no ROP or stage 1 ROP, eye examinations were repeated every 2 weeks. For those with stage 2 ROP, exams were repeated every 1-2 weeks, and stage 3 every 1 week or less. Eye examinations were repeated until subjects' retinas were fully vascularized and the ROP had regressed. For purposes of data analysis, infants were divided into 2 groups: infants without ROP and infants with ROP. Data were recorded retrospectively and the presence of retinopathy was graded according to the International Classification of ROP. Maternal and obstetric characteristics were documented including maternal age, maternal haemorrhage, maternal prolonged rupture of membrane (PROM), preeclampsia, eclampsia, maternal diabetes mellitus, and antenatal dexamethasone administration. Demographic data collected also included infants' GA, BW, and gender. Clinical data retrieved included APGAR scores at 1 minute and 5 minutes after birth, and the presence of respiratory distress syndrome (RDS), air leak, sepsis, apnea, and patent ductus arteriosus (PDA), as well as ibuprofen, aminophylline or surfactant usage. Respiratory data included type of respiratory support, and the durations on oxygen therapy, continuous positive airway pressure (CPAP) usage or mechanical ventilation.

Prematurity was defined as infants with GA < 37 weeks. Gestational age was ascertained based on maternal dates and early ultrasonographic dating in the first trimester. All infants were scored clinically using Ballad scores. If there was a discrepancy of more than 2 weeks between the scored dates and maternal dates, the GA determined by scoring was taken. Respiratory distress syndrome was diagnosed based on clinical and radiological evidence. Sepsis was diagnosed by clinical examination and/or microbiological culture. Clinical sepsis was based presence of three or more of the following: apnea, difficulty of breathing, cyanosis, tachycardia or bradycardia, shock, irritability, lethargy, hypotonia, seizures, abdominal distention, vomiting, dietary intolerance, gastric residue, thermal instability, and general poor appearance. The presence of PDA was diagnosed clinically and confirmed by two-dimensional echocardiography. Adequate antenatal administration of dexamethasone was defined as the completion of 2 doses given 12 hours apart with the second dose administered more than 24 hours prior to delivery .

Statistical analysis was performed using the statistical package for social sciences (*SPSS 15*) software. Univariate comparison of risk factors between the groups with and without ROP were evaluated using Fisher's exact test and independent t-test with a significance level of $P<0.05$.

Results

During the study period, 48 infants (26 males and 22 females) met the criteria and underwent ROP screening exams. Retinopathy of prematurity was present in 6 (12.5%) subjects, of whom 2 (4.2%) subjects had stage 3 ROP and required surgery (**Figure 1**).

Retinopathy of prematurity was inversely correlated with BW and GA, and was found in infants with GA < 30 weeks, and BW < 1250 g. Mean BW was 935 (SD 224.86) g in ROP infants and 1425.60

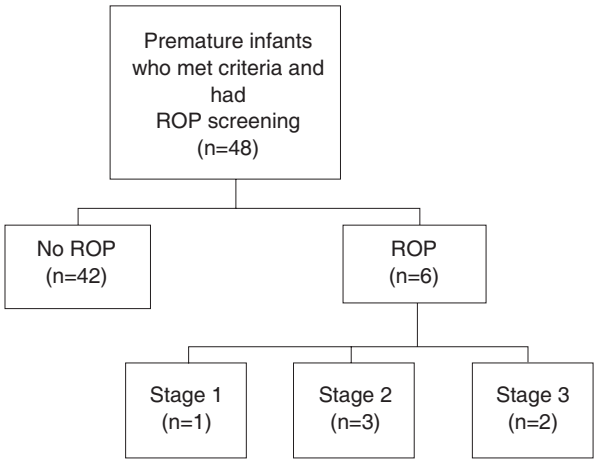

Figure 1. Schematic diagram of the distribution of infants in the study

Table 1. Characteristics of subjects

Characteristics	No ROP group (n=42)	ROP group (n=6)	P value
Sex, n (%)			
Male	21 (50.0)	5	0.199
Female	21 (50.0)	1	
Birth weight, n (%)			
<750 g	1 (2.4)	2	
750 – 999 g	5 (11.9)	1	
1,000 – 1,249 g	3 (7.1)	3	
1,250 – 1,499 g	15 (35.7)	0	
>1,500 g	18 (42.9)	0	
Mean birth weight (SD), gram	1,425.6 (323.4)	935 (224.8)	0.001
Gestational age, n (%)			
24 - <26 weeks	1 (2.4)	2	0.004
26 - <28 weeks	4 (9.5)	1	
28 - <30 weeks	7 (16.7)	3	
30 - <32 weeks	18 (42.8)	0	
32 – 34 weeks	12 (28.6)	0	

(SD 323.491) g in infants without ROP, a significant difference (P<0.05). There was not a statistically significant difference in gender between the 2 groups (5 males and 1 female had ROP; 21 males and 21 females had no ROP) (**Table 1**).

Table 2 shows the maternal and obstetric factors of our subjects by group. Maternal age, maternal PROM, antepartum haemorrhage, preeclampsia, eclampsia, maternal diabetes mellitus (DM), antenatal dexamethasone administration, and method of delivery were not significantly different between infants with ROP and those without ROP. We used the independent t test for maternal age, and Fisher's exact test for other variables.

Premature infants' factors are summarized in **Table 3**. Infants with ROP had significantly lower mean APGAR scores at the 5th minute than infants without ROP, 7.33 (SD 0.82) vs. 8.21 (SD 1.18), respectively (P<0.05). However, mean APGAR scores at the 1st minute were not significantly different between the two groups. Occurrence of RDS, sepsis, apnea, blood transfusion, and receiving of aminophylline were significantly greater in those who developed ROP (P<0.05). There was no significant differences in air

Table 2. Comparison of maternal and obstetric factors between groups

Variables	No ROP group (n=42)	ROP group (n=6)	P value
Mean maternal age (SD), years	29.98 (4.331)	28.67 (2.805)	0.478
Maternal PROM, n (%)	14 (33.3)	0	0.161
Antepartum haemorrhage, n (%)	2 (4.8)	0	1.000
Multiple births, n (%)	19 (46.3)	4	0.416
Preeclampsia, n (%)	4 (9.5)	1	0.503
Eclampsia, n (%)	1 (2.4)	1	0.237
Maternal DM, n (%)	2 (4.8)	0	1.000
Antenatal dexamethasone, n (%)	37 (88.1)	3	0.05
LSCS, n (%)	41 (97.6)	6	1.000
Spontaneous labour, n (%)	1 (2.4)	0	1.000

PROM: prolonged rupture of membranes; LSCS: lower segment caesarean section; DM: diabetes mellitus

Table 3. Risk factors in subjects with or without ROP

Variables	No ROP group (n=42)	ROP group (n=6)	P value
Mean APGAR score at 1st min (SD)	6.62 (1.51)	5.5 (1.52)	0.138
Mean APGAR score at 5st min (SD)	8.21 (1.18)	7.33 (0.82)	0.048
Respiratory distress syndrome, n (%)	19 (45.2)	6	0.023
Air leak, n (%)	2 (4.8)	0	1.000
Surfactant usage, n (%)	2 (4.8)	1	0.336
Patent ductus arteriosus, n (%)	10 (23.8)	4	0.052
Sepsis, n (%)	8 (19.0)	5	0.004
Apnea, n (%)	13 (31.0)	6	0.002
Blood transfusion, n (%)	4 (9.5)	5	0.0001
Ibuprofen usage, n (%)	5 (11.9)	3	0.05
Aminophylline usage, n (%)	13 (31.0)	6	0.002
CPAP usage, n (%)	16 (38.1)	5	0.073
Ventilator, n (%)	6 (14.3)	2	0.258
Oxygen, n (%)	25 (59.5)	6	0.077
Mean CPAP duration (SD), days	0.76 (1.12)	1.83	0.036
Mean ventilator duration (SD), days	0.43 (1.21)	1.83	0.305
Mean oxygen duration (SD), days	3.81 (5.22)	14	0.046

CPAP: continuous positive airway pressure

leak, patent ductus arteriosus, as well as ibuprofen or surfactant administration in the two groups.

Oxygen requirement and respiratory support such as ventilator or CPAP were not significantly different in the two groups. However, the duration of oxygen requirement and duration of CPAP usage were significantly longer in infants with ROP than in those without ROP ($P < 0.05$).

Discussion

Retinopathy of prematurity continues to be an important cause of potentially preventable blindness worldwide.[9] Our study evaluated the incidence and risk factors of ROP in premature infants. We found that the ROP incidence was 12.5%, with 2% of our subjects in stage 1, 6.25% in stage 2, and 4% in stage 3. The 2 subjects with stage 3 ROP required surgery. In Singapore, ROP incidence was reported to be 29.2% in very low birth weight (VLBW) infants. Of these, 49% had stage 1, 24% had stage 2, and 27% had stage 3 or more.[10] A study in Taiwan reported that ROP was identified in 190 (37.8%) of 503 live births with BW < 1500 g and GA < 32 weeks; 12.1% of their subjects had stage 1, 7.2% had stage 2, 16.1% had stage 3, 2.2% had stage 4 and 0.2% had stage 5.[11] The incidence ROP is lower in our study compared to the studies in Singapore and Taiwan, this may be caused by more babies with BW less then 1250 g in Singapore and Taiwan studies, while in our study more babies were above 1250 g.

The CRYO – ROP multicenter study showed that in infants with BW < 1251 g, 65.8% developed ROP to some degree. Furthermore, ROP incidence was 81.6% in infants < 1000g.[12] In India, ROP incidence was reported to be 27%,[13] while that in Norway was 10.1%,[14] Finland was 17.4%[15] and Australia was 16%.[16] In Connecticut, USA, the incidence of ROP was 21.3% for any stage, and no ROP was noted in infants born at GA >32 weeks.[17]

We found that higher incidence of ROP was significantly associated with lower BW and GA, similar to a previous report.[11] In our subjects, ROP was only found in infants with BW <1250 g and GA < 30 weeks. No ROP was detected in infants with GA $\geq$ 30 weeks or BW $\geq$ 1250 g. A study in Singapore reported that no ROP was detected in infants with GA > 33 weeks.[10] A Scottish study found ROP in 8% of infants with BW > 1251 g and 12.5% in those with GA > 30 weeks.[18] Another study reported ROP was still found in infants with BW > 2000 g and GA $\geq$ 34 weeks.[19] The incidence of ROP was not significantly different between genders in our study, similar to previous reports by the ROP Cooperative Group.[20,21] A New Zealand study reported that male gender contributed to severe ROP, but in Australia female gender was reported to be significantly associated with ROP.[16,22]

Antenatal betamethasone has been reported to reduce the incidence of ROP. A previous study reported a decrease in the ROP incidence of 36.1% compared to the international incidence of 57.2% for the Vermont-Oxford Network Database (VOND) in 1997 ($P < 0.001$). In contrast, we found that antenatal steroid (dexamethasone) administration did not reduce ROP incidence, similar to previous reports from Singapore and Taiwan.[10,11] Filho *et al*. reported that maternal preeclampsia lowered the risk for occurrence of any stage of ROP and severe ROP in VLBW infants.[24] However, our findings showed that the occurrence of maternal preeclampsia was not significantly different in the two groups.

A report from Oman noted that BW, GA, apnea, blood transfusion, mechanical ventilation, metabolic acidosis, total parenteral nutrition (TPN), intraventricular hemorrhage (IVH), and sepsis were associated with development of ROP.[25] An Australian study reported days of ventilation and multiple births to be significantly associated with ROP.[16] A Connecticut, USA study found only GA and days on supplemental oxygen therapy to be significantly associated with the development of ROP.[17] A previous study in Singapore found that hypothermia, lower GA, lower BW, lower APGAR scores at 1 and 5 minutes after birth, RDS, air leak, PDA, and septicemia, as well as chronic lung disease were associated with the development of ROP.[10] A study in Taiwan reported that respiratory distress syndrome, chronic lung disease, PDA, surfactant usage, indomethacin administration, sepsis, blood transfusion, and necrotizing enterocolitis were associated with ROP.[11] Another study from India found blood transfusion and clinical sepsis to be independent risk factors of ROP.[13] Our study revealed that ROP had a statistically significant association with lower APGAR score at 5 minutes, RDS, sepsis, apnea, blood transfu-

sion, aminophylline administration, as well as longer duration of oxygen therapy, and CPAP usage.

Our study has several limitations, the first is our data was based on medical records and we have only small amount of subjects.

In conclusion, the incidence of ROP in premature infants is 12.5% in our study. Retinopathy of prematurity is associated with lower BW, lower GA, lower APGAR score at 5 minutes, RDS, sepsis, apnea, blood transfusion, aminophylline administration, as well as longer duration of oxygen therapy, and CPAP usage.

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