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Screening for retinopathy of prematurity at Cipto Mangunkusumo Hospital, Jakarta, Indonesia – a preliminary report

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Background: To report the incidence of retinopathy of prematurity (ROP) at Cipto Mangunkusumo Hospital, Indonesia, and its relation to several risk factors. The results of treatment are also reported.

Materials and Methods: A hospital-based prospective-cohort study in 33 infants in the neonatology ward of Cipto Mangunkusumo Hospital, Jakarta, Indonesia, who were referred for ROP screening from December 2003 to December 2004 was performed. Risk factors such as gestational age (GA) at birth ≤ 32 weeks, birth weight (BW) ≤ 1500 g, duration of oxygen (O_2) therapy more than 7 days, gender, birth status, the presence of clinical sepsis, respiratory distress syndrome (RDS), apnea, asphyxia, and maternal pre-eclampsia / eclampsia were analyzed using the chi-square test and multivariate analysis.

Results: Of the total of 33 cases, ROP at any stage of disease was found in 30.3%. Infants with ROP were significantly smaller (mean ± SD of 1397 ± 153.5 g vs. 1610 ± 218.8 g, p = 0.009), but not significantly younger (mean ± SD of 31.7 ± 2 weeks vs. 33.3 ± 2 weeks, p = 0.058) than infants without ROP. Logistic regression showed that low birth weight was not a significant risk-factor for ROP. Asphyxia was found to be the only significant risk factor for the occurrence of ROP (p = 0.021, OR = 13.525). Laser photocoagulation or cryotherapy was performed in 2 out of 3 threshold ROP cases, but the outcomes were still unsatisfactory.

Conclusions: Our results are similar to those reported from previous studies in other developing countries, although in this study young gestational age and low birth weight were not associated with the risk of ROP. Further studies in a larger sample are required to confirm these findings and to establish effective screening guidelines.

Key words: ROP, screening, risk factors, asphyxia, treatment, Indonesia

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative retinopathy of premature and low-birth weight infants (1, 2). ROP has been acknowledged as one of the causes of blindness in children in developed countries, and has emerged as a problem in developing countries as well, along with the increased survival of younger and smaller infants (3). Based on various screening guidelines, the incidence of ROP worldwide is reported to be 10–65.8% (4). The major risk factors in ROP are early gestational age (GA) at birth and low birth weight (BW). Oxygen (O_2) therapy is also a principal, although not proven to be the only causative factor. Other related factors include sepsis, repeated blood transfusions, respiratory distress syndrome (RDS), and multiple birth (4–10).

The World Health Organization (WHO) has categorized ROP as an avoidable disease, therefore screening, which is usually performed in a tertiary care, is important (3). So far, in Indonesia there have been no published reports on ROP, and an effective screening guideline has not been established yet. Meanwhile, the awareness for screening and treatment for ROP has increased among both pediatricians and ophthalmologists since the last five years, and for this reason a study on ROP in Indonesia is urgently required. A preliminary study to report the incidence, severity, risk factors and results of treatment for ROP is conducted in a tertiary care hospital in Indonesia. The outcomes may be used in establishing the screening guidelines for ROP in Indonesia.

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SUBJECTS AND METHODS

Design

This is a cohort study conducted at Cipto Mangunkusumo Hospital (a general hospital) from December 2003 until December 2004.

Subjects

All newborn premature infants referred by pediatrics department for ROP screening, who met inclusion criteria such as GA at birth less than 37 weeks, BW not exceeding 2000 g (11), and complete medical record.

Risk factors

Additional to GA at birth and BW, there were several other prenatal and neonatal variables reviewed for their association with the incidence of ROP, which included gender, birth status (single / multiple), duration of O_2 treatment, the presence of clinical sepsis, RDS, apnea, asphyxia and maternal pre-eclampsia / eclampsia.

Examination

All screenings took place at the neonatology ward and were performed by the authors. Infants underwent fundus examination by indirect ophthalmoscopy with +20 D condensing lens. The pupils were dilated with 0.5% tropicamide eyedrops. An infant eyelid speculum was placed during each examination, after administration of topical anesthesia with 0.5% tetracain hydrochloride. Scleral indentation was done only if necessary, to view the retina periphery.

Diagnosis of ROP

Observations were classified according to the International Classification of Retinopathy of Prematurity (ICROP). The ICROP defines retinopathy by location, extent, stage, and plus disease (12).

Zone I is a 60^0 circular area centered on the optic disc and extending from the disc to twice the distance between the disc and the macula. Zone II is a ring concentric to Zone I, which extends to the nasal ora serrata. Zone III is the remaining crescent of temporal retina (12).

The extent of ROP is described by the number clock hours of the retina involved (12).

The staging in ROP describes progressive changes in the retinal vessels. Stage 1 is characterized by a demarcation line between the normal retina and the non-vascularized retina. In stage 2 the demarcation line has progressed into an intraretinal ridge of scar tissue and new vessels with width, height, and volume. Stage 3 shows an increased size of the vascular ridge with the growth of fibrovascular tissue on the ridge and extending out into the vitreous. Fibrous scar tissue is beginning to form in this stage, with attachments between the vitreous gel and the ridge. Stage 4 refers to a subtotal retinal detachment. The scar tissue is associated with the fibrovascular ridge contracts, pulling the retina away from the wall of the eye. In stage 4A, the detachment does not include the macula while in stage 4B the macula is detached. Stage 5 ROP implies a complete retinal detachment, with the retina pulled into a funnel-shaped configuration (12).

Plus disease is characterized by dilation and tortuosity of the blood vessels at the posterior pole. It also includes the growth and dilation of abnormal blood vessels on the surface of the iris, rigidity of the pupil, and vitreous haze. The presence of plus disease suggests a more fulminant or rapidly progressive course (12).

Threshold ROP is zone I stage 1, 2 or 3 ROP with plus disease, or stage 3 ROP with plus disease in zone I or II, involving at least 5 clock hours contiguously or 8 clock hours cumulatively (2, 5). If threshold ROP is reached, treatment within 72 hours is mandatory, either with cryotherapy or laser photocoagulation (13). A condition requiring close observation for progression to threshold stage is pre-threshold ROP, defined as zone I of any stage less than threshold disease, zone II with stage 2 or stage 3 ROP without plus disease, or stage 3 ROP with plus disease less than the criteria for threshold ROP (5,10).

Management

The initial examination should be performed between 4–6 weeks of chronologic (postnatal) age, or 31–33 postconceptual (GA + chronologic) age, whichever is later (12). If the initial examination did not reveal ROP, the infant was recommended to be re-evaluated before discharge, or after reaching full-term age (40 weeks) to observe complete retinal vascularization. Infants showing zone III ROP were recommended for re-evaluation every two weeks, until they reached complete retinal vascularization. Infants showing pre-threshold disease were recommended for weekly examination until there were signs of resolution or progression to threshold disease. Treatment with cryotherapy or laser photocoagulation was planned within 72 hours for infants with threshold ROP.

Cryotherapy involved placing a very cold probe on the outside wall of the sclera and freezing until an ice ball forms on the retinal surface. Usually, 30–50 spots of cryotherapy were applied to the entire avascular area anterior to the neovascular ridge (14).

Laser photocoagulation using argon or diode lasers, was performed using an indirect laser delivery system. Laser was also aimed at the avascular retina anterior to the ridge, usually applying 600–1000 laser spots. Recently, laser photocoagulation has become the preferred treatment for ROP (13,14).

Data collecting and analysis

All findings were documented into ROP consultation forms (with schematic fundus drawings), and ROP log book. All data were summarized into a main table. Computerized data processing was done using SPPS statistical test. Univariate analysis using Student's t test

was used in comparing the mean gestational age at birth and birth weight between infants with and without ROP, while the Fisher exact test was used for risk factors in infants with ROP. The difference was considered statistically significant if the p value was < 0.05. Multivariate analysis using logistic regression was performed for variables showing a significant value ($p < 0.05$).

RESULTS

Thirty-three screened infants met inclusion criteria. The initial examination took place between 1–8 weeks of the infants' chronological age.

The mean GA of all enrolled infants was 31.6 weeks, with a range of 28–36 weeks. Mean BW was 1545 g, with a range of 1100–1940 g.

Bilateral ROP at any stage was found in 10 infants (30.3%). The relation between the incidence of ROP and the distribution of GA at birth is presented in Fig. 1, and the relation between the incidence of ROP and the distribution of BW is shown in Fig. 2.

The number of infants with ROP was highest in GA at birth of 32 weeks, but the incidence was higher in younger infants (28 and 29 weeks). The majority of infants with ROP had BW of 1250–1500 g. However, the proportion of infants with ROP was highest in the 1000–1250 group.

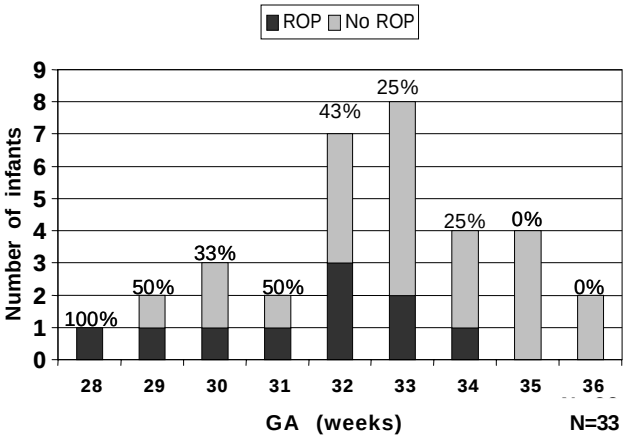

Fig. 1. Incidence of retinopathy of prematurity according to distribution of gestational age at birth

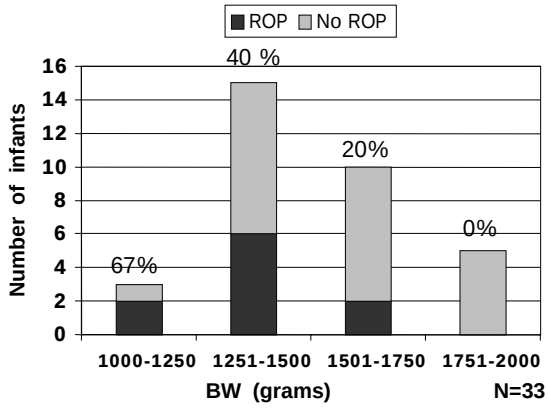

Fig. 2. Incidence of retinopathy of prematurity according to distribution of birth weight (BW)

A comparison of mean gestational age at BW among infants with and without ROP is pictured in Table 1 which shows an association between gestinational age and birth weight with the incidence of ROP. Infants with ROP were significantly smaller ($p = 0.058$) than infants without ROP.

Table 1. **Comparison of gestational age and birth weight between infants with and without retinopathy of prematurity**

Risk factors	Mean (SD) in infants with ROP	Mean (SD) in infants without ROP	p value
Gestational age at birth (weeks)	31.7 (2.06)	33.3 (2.06)	0.058
Birth weight (grams)	1397 (153.5)	1610 (218.8)	0.009
			N=33

For screening criteria, GA at birth was then divided into two groups: 32 weeks or less, and more than 32 weeks. BW was also divided into two groups: 1500 g or less, and more than 1500 g. This division was based upon the majority of screening criteria in published reports from other Asian countries. The incidence of ROP in these groups is shown in Table 2.

Using the criteria of GA at birth of 32 weeks or less and BW of 1500 g or less as screening guidelines, the incidence of ROP was noticeably higher. However, the difference was significant only between BW groups. Table 2 shows that ROP was still present in infants born with GA more than 32 weeks and BW more than 1500 g. Moreover, Fig. 1 reveals that ROP was still present in infants born as old as 34 weeks and in infants weighing 1600 g.

Using logistic regression, asphyxia was statistically proven as a risk factor for ROP ($p < 0.5$, OR = 13.525) However, the incidence of ROP was markedly higher in female infants, RDS, and apnea. Birth status, duration of O_2 therapy, presence of clinical sepsis and history of maternal pre-eclampsia / eclampsia were not statistically proven to be related to ROP.

Pre-threshold ROP, stage 4 ROP and stage 5 ROP were not encountered in this study. Threshold ROP was discovered in 3 infants, i. e. 30% of the ROP group or 9.1% overall. Summarized details on these ROP patients are displayed in Table 3 (threshold ROP cases are shaded in gray).

The mean (SD) GA at birth in infants with threshold ROP was 29 (1) weeks, versus 32.4 (1.6) weeks in infants not reaching threshold ROP, but this difference was not statistically significant.

Follow-up was only achieved in 7 cases. Among them, three showed signs of ROP regression. The other two cases also underwent re-examination, but with missing follow-up data..

Table 2. **Relations between incidence of ROP and other risk factors**

Risk factors	No. of infants with ROP	No. of infants without ROP	Total	p value	OR
Gender:					
male	2 (16.7%)	10 (83.3%)	12	NS	
female	8 (38.1%)	13 (61.9%)	21		
Birth status:					
single	8 (32%)	17 (68%)	25	NS	
multiple	2 (25%)	6 (75%)	8		
Duration of O_2 treatment:					
≤ 7 days	0 (0%)	7 (100%)	7	NS	
> 7 days	10 (38.5%)	16 (61.5%)	26		
Clinical sepsis:					
present	8 (30.8%)	18 (69.2%)	26	NS	
not present	2 (28.6%)	5 (71.4%)	7		
RDS:					
present	2 (66.7 %)	1 (33.3%)	3	NS	
not present	8 (26.7 %)	22 (73.3%)	30		
Apnea:					
present	1 (50%)	1 (50%)	2	NS	
not present	9 (29%)	22 (71%)	31		
Asphyxia:					
present	3 (75%)	1 (25%)	4	0.026	13.525
not present	7 (24.1%)	22 (75.9%)	29		
Pre-eclampsia / eclampsia					
present	4 (30.7%)	9 (69.3%)	13	NS	
not present	6 (30%)	14 (70%)	20		
Gestational age at birth:					
≤32 weeks	6 (42.6%)	8 (57.4%)	14	NS	
>32 weeks	4 (19.0%)	15 (81%)	19		
Birth weight:					
≤ 1500 g	8 (47%)	9 (53%)	17	0.048	1.005
> 1500 g	2 (12.5%)	14 (87.5%)	16		
					N=33

NS: non-significant.

Treatment was carried out in 2 out of 3 cases with threshold ROP; one infant underwent laser photocoagulation and the other underwent cryotherapy. The results were unsatisfactory. For the infant who underwent laser photocoagulation on both eyes, the procedure was performed 12 days after diagnosis, but she developed vitreous bleeding in the right eye and progression to stage 4 ROP in the left eye. In the other infant, cryotherapy was the preferred method of treatment, because the small and rigid pupils did not allow laser photocoagulation. Cryotherapy was carried out on both eyes 4 days after diagnosis, with a complication of heavy eyelid swelling which inhibited post-operative eye examination. Unfortunately, this infant died of severe sepsis.

DISCUSSION

The screening guidelines for ROP depend on the epidemiology and the neonatal care unit in each population. In order to establish screening guidelines, it is recommended that each population should have baseline data which include incidence, risk factors, management, and outcomes.

In this preliminary study, the incidence of ROP was 30.3%. This percentage was within the range of incidences reported worldwide. It is lower than the incidence of 65.8% reported by the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, which used the criteria of BW less than 1251 g (5). The incidence in this study was closer to those reported from several Asian countries. Trinavarat et al. (9) obtained an incidence of 13.6% for ROP in Thailand. In Taiwan, Yang et al. (12) reported an incidence of 25%. Theng et al. (15) and Leo et al. (16) in Singapore revealed the ROP incidence of 14.2% and 34.4%, respectively.

The mean GA at birth and BW of all the screened infants in this study (31.6 weeks and 1545 g) were also similar to those from the report by Trinavarat et al. (9) in Thailand (31.8 weeks and 1416 g) and Yang (6) from Taiwan (31.6 weeks and 1594 g).

In previous studies, low BW and early GA well shown as the two major risk factors for ROP (1, 2, 4–9). Although

Table 3. **Characteristics and follow-up of infants with ROP**

No.	Name of patient	Gender	Gestational age at birth (weeks)	Birth weight (grams)	Severity of ROP (OD/OS)	Treatment	Remarks
1.	F	M	32	1450	Zone III Stage 1 / Zone III Stage 1	-	Regressed
2.	Sj	M	33	1600	Zone III Stage 1 / Zone III Stage 1	-	NA
3.	DR	F	34	1300	Zone III Stage 1 / Zone III Stage 1	-	NA
4.	Yn	F	31	1500	Zone III Stage 1 / Zone III Stage 1	-	No follow-up
5.	Sr II (Twin)	F	32	1320	Zone III Stage 1 / Zone III Stage 2+	-	Regressed
6.	Em	F	33	1600	Zone III Stage 1 / Zone III Stage 2	-	No follow-up
7.	G	F	32	1500	Zone III Stage 2 / Zone III Stage 2	-	Regressed
8.	Sy	F	29	1160	Zone II Stage 3+ / Zone II Stage 3+	Laser Photocoagulation	Progression
9.	Fr I (Twin)	F	30	1240	Zone II Stage 3+ / Zone II Stage 3+	Cryotherapy	Died (sepsis, apnea)
10.	Yu	F	28	1300	Zone II Stage 3+ / Zone II Stage 3+	-	No follow-up

NA: not available.

not confirmed statistically in this study, ROP was found in younger and smaller premature infants and there were increased incidences of ROP corresponding to the earlier GAs at birth and the lower BWs.

Oxygen treatment for more than 7 days was given to all infants with ROP, but its significance was not confirmed by statistical tests. In previous reports, O_2 saturation levels were monitored by pulse oxymetry (14). However, at the time of this study, the majority of infants' O_2 saturation levels were not monitored by pulse oximetry.

Sepsis was identified as a risk factor in previous reports (6,13), but it was not proven to be a risk factor in this study. This may be caused by the fact that sepsis was suspected in any decreased condition of the infant, instead of blood culture findings. In contrast with other reports where there was no gender predominance, this study revealed a higher incidence of ROP among female infants. This finding may be related to the larger number of screened female infants (21 females vs 12 males).

Asphyxia was shown to be a statistically significant factor for ROP. Logistic regression analysis shows that the risk for an infant who has suffered from asphyxia to develop ROP is 13 times greater than of infants with no history of asphyxia. This may be caused by the hypoxic condition that occurs in asphyxia. However, other conditions which may also lead to hypoxia, such as RDS and apnea, were not proven to be linked with the occurrence of ROP.

The other proposed risk factors including multiple birth and maternal pre-eclampsia / eclampsia were not related to the incidence of ROP in this study, and this is in line with previous reports (6, 10).

The management of infants with ROP, which implies the method and setting of examination and the strategy for screening and follow-up, was carried out according to protocols from previous reports, However, the time of initial examination in this study has not completely followed the general protocol (4–6 weeks after birth, or between 31–33 of chronological age) (12). Initial examination in a few cases was performed earlier (as early as 1 week) if the infant had reached postnatal age of 31–33 weeks, or later (as late as 8 weeks) if the condition of the infant was unstable or did not allow to endure any maneuvering during examination.

Screening should be based on local criteria, which includes all babies at risk for ROP, without missing any case. This study tried to determine whether the criteria of GA at birth of 32 weeks or less and BW of 1500 g or less can cover all cases with ROP. It has been revealed that there are still cases of ROP beyond those criteria. This fact may suggest that ROP in Indonesians may still be found in relatively older and larger infants compared to other reports worldwide.

The severity of ROP in this study, represented by the incidence of threshold ROP (9.7%), was higher than in other reports. Allegaert et al. (7) in Belgium reported an incidence of 6.4% in infants with BW less than 1500 g. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) found a threshold ROP incidence of 6.0% of total population (5). The finding of threshold disease in this study corresponds to the lowest and youngest of infants with ROP. Despite treatment, the outcomes were poor. Threshold ROP requires treatment within 72 hours, which could not yet be fulfilled in this study for various reasons such as unstable clinical condition and financial considerations.

In conclusion, the incidence of ROP in Cipto Mangunkusumo Hospital, Jakarta, Indonesia is similar to that in other reports, especially from Asian countries. Asphyxia was proven as a risk factor. Early GA at birth and low BW seem to be major risk factors, though not confirmed statistically. O_2 therapy, sepsis, female gender, RDS, and apnea were not established as risk factors. GA at birth of 34 weeks or less and BW of 1600 g or less may be proposed as criteria for the screening guidelines for ROP in Indonesia.

These findings are limited by the short period, small number of subjects, and bias in variables. Further studies with a larger number of subjects, with appropriate statistical risk analysis are required to form the appropriate screening guidelines.

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