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Retinopathy of Prematurity

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RETINOPATHY OF PREMATURITY

How to Prevent Retinopathy of Prematurity in Indonesia?

Johanes Edy Siswanto

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Retinopathy of Prematurity

How to prevent retinopathy of prematurity in
Indonesia?

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Dedicated to Valentina, Jedrick, Renzo, Benzi, and my parents

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CHAPTER 1

Introduction

On February 14, 1941, Dr. Stewart Clifford, a pediatrician in Boston, USA, made a house call to check on one of his patients, a three-month-old daughter of a colleague. The girl had been born several weeks preterm, weighing just four pounds at birth, but had been doing well in the months since her birth. There were roving nystagmus and opacities in both eyes. The girl was completely blind. A few months later, there was a seven-month-old baby that he found had the same symptoms. And just as with the prior case, the child had been born preterm. That baby had also become blind. Clifford contacted Dr. Theodore Terry, professor of ophthalmology at Harvard Medical School, to look into his cases. In 1942 Terry described “fibroblastic overgrowth of vascular sheath behind the crystalline lens” in five ex-preterm infants, and the disease was named Retrolental Fibroplasia (RLF). (1) Soon after this report, it became clear that eye problems, leading to blindness, was a major problem in ex-preterm infants. In 1945 Terry reported that Dr. Stewart Clifford had found that 12 percent of the ex-preterm infants of less than 1360 grams can become blind. The cause of the disease remained unclear. (2, 3)

In 1952 Dr. Zacharias published a long list of potential causes of RLF in a review (Table 1).

Table 1. Putative causes for Retrolental Fibroplasia.

-
- A. *Factors relating to the parents*
 - 1. Placental deformities
 - 2. Uterine bleeding
 - 3. Antenatal history of all mothers
 - B. *Factors relating to the infant*
 - 1. Season
 - 2. Multiple birth
 - 3. Sex distribution
 - 4. Congenital anomalies
 - 5. Condition of the infant at birth
 - 6. Pediatric management
 - a. Light
 - b. Feeding

- c. Blood transfusions
- d. Vitamin A deficiency
- e. Water-miscible vitamin supplements and iron
- f. Vitamin E deficiency
- g. Anoxia and oxygen
- h. Infection
- i. Hemorrhagic tendency of preterm infants
- j. Delayed retinal coaptation
- k. Uncontrolled neovascularization
- l. Susceptibility due to prematurity
- m. Noxious stimuli
- n. Uveitis
- o. Ocular hypertension
- p. Growth influences

Source: Adapted from L. Zacharias. Retrolental fibroplasia: A. survey. Am J Ophthalmol 1952: 35;1426-54. (4)

Oxygen was not included in this list, as it was not considered as a potential cause. Remarkably, a survey done in three hospitals in Boston, USA, found a concurrent increase in the rate of Retrolental Fibroplasia with iron supplementation, the use of water-soluble vitamins, and oxygen (Fig. 1). The authors of this paper concluded that the correlation between the rise in RLF and oxygen was less striking than the use of iron supplementation and water-soluble vitamins.

Fig.1 Correlation between the frequency of RLF and three treatments in the premature nursery at the Boston Lying-In Hospital, 1938-1947; its occurrence tracked most closely with iron therapy (ferrous sulfate). (5) * Days in oxygen, drops of water-miscible vitamins, and grams of ferrous sulfate.

That treatment with oxygen might be involved in the development of RLF became clear from a study done in Australia between 1948 and 1950. (6,7)

In that – small- study, a higher incidence of RLF was found in infants cared for in a high compared to a moderate oxygen treatment group. This finding, however, was disputed because at the same time papers were published that RLF was caused by a lack of oxygen. An animal model seemed to support this hypothesis. (8,9)

Around 1950, new incubators were introduced in which it was possible to provide up to 60% oxygen. The use of these incubators, also named “oxygen cots,” has undoubtedly contributed to the significant increase in RLF cases in the early 1950s. (6)

In 1952 a controlled trial was started to evaluate the potential risk of oxygen for the development of RLF. The results of this study are shown in Table 2.

Table 2. Incidence of Retroental Fibroplasia in 181 Premature Infants in Melbourne, Australia, 1948-1950

Year	High Oxygen		Moderate Oxygen	
	Therapy Group		Therapy Group	
	Number	Cases	Number	Cases
	of infants	of RLF	of infants	of RLF
1948	36	6	11	2
1949	32	10	23	1
1950	55	7	24	1
Total	123	23 (8,7%)	58	4 (6.9%)

Source : Adapted from K. Campbell. Intensive oxygen therapy as a possible cause of retrolental fibroplasia: A clinical approach. Med J Aust 1951;2:48. (7)

There was a striking lower incidence of RLF in the lower oxygen group. This, however, had no direct effect on the then accepted treatment for small preterm infants, the administration of 60% oxygen in the incubator. (10,11)

Only after least three more studies and a period of a few years came restrictions in the use of oxygen. (12-15) Still, the notion of a “critical concentration of oxygen of 40%” was accepted as a fact by -almost- all pediatricians. Pediatric textbooks up to 1955 advised using high oxygen concentration in the incubator for small preterm infants. Textbooks published after 1955 recommended that “the least amount of oxygen necessary for survival be given to the preterm infant.”

At the beginning of the 1960s, there was a very optimistic opinion about RLF; this disease was so-called “conquered.” RLF was, according to the opinion at that time, caused by the overuse of oxygen. Reducing the use of oxygen would lead to the disappearance of the disease. Papers were also published, however, showing an increase in mortality related to the restricted use of oxygen. Also, an increase in neurological damage was seen in infants exposed to a restricted amount of oxygen. In the 1960s, efforts were started

to keep infants with Hyaline Membrane Disease alive. The only available treatment was the use of oxygen, so the use of high oxygen concentration in the incubator returned. Therefore a large multicenter study was done to establish the safe level of PaO₂ and the duration of exposure to oxygen that would result in RLF. This study, however, could not identify a correlation between PaO₂ and RLF, probably due to the fact that only intermittent measurements of PaO₂ were done. (5,15-17)

In the 1970s and 1980s, it became possible to measure non-invasive, transcutaneous, first the PaO₂ and later the oxygen saturation, SaO₂. This was a major step forward because the amount of oxygen given could be tailored to the infant's oxygen concentration. (18-19) Many large-scale studies have been done to find a safe level of oxygen saturation, levels that would prevent RLF but at the same time would not increase death or neurological damage. Several studies, such as STOP-ROP, SUPPORTROP, and BOOST II, have evaluated the effect of different saturation levels in preterm infants. (20-22) A saturation level of <92% might reduce the risk of ROP but at the expense of a higher mortality rate. Based on these studies' partly conflicting results, it is now advised to set saturation limits in preterm infants at 90–95%. (23)

From the 1980s, again, an increase in the incidence of RLF, or Retinopathy of Prematurity (ROP) as it was named at that time, occurred. With advances in the care of tiny and sick newborn infants, more of these infants survived. The increase in ROP was seen in infants born at a very low gestational age, 24-28 weeks. The disease was seen even in infants who did not receive supplemental oxygen. These findings indicate that the main risk factor for the development of ROP is a very low gestational age, with oxygen supplementation as an important additional factor. Studies from the USA showed an incidence of all stages of ROP, ranging from 40% in infants with a birth weight of 1101–1200g to 90% in infants of 501–600g. (24-25) A correlation was found with gestational age, with an increase from 35% at a gestational age of 31 weeks to 95% at 24 weeks. Data from Sweden (Larsson et al. and EXPRESS study) showed an incidence of all stages of ROP, ranging from 18% (birth weight <1500 g), 34% (birth weight <1000 g), and increasing up to 61% (for infants with a gestational age <27 weeks). (26-27)

Over the last decade, the third increase in ROP is seen, especially in Low and Middle-Income Countries (LMIC). (28,29) This is related to the start of neonatal intensive care in these countries, while systems to control the oxygen saturation, as well as the amount of oxygen given, are not always available. In several health facilities, it is only possible to supply 100% oxygen without the possibility to measure the resulting oxygen saturation in the infant. In this thesis, we will analyze the incidence of ROP in Indonesia, an LMIC, investigate risk factors for the development of ROP, and advise on how to prevent ROP.

Pathophysiology

Retinopathy of prematurity can develop when babies are born before their retinal blood vessels are fully developed. In babies born at full term (between 37 and 42 weeks of gestation), the retinal blood vessels are fully developed and reach the retina's edge: the Ora Serrata (Figure 1). In babies born preterm (before 37 weeks), the retinal blood vessels are not fully formed and do not reach the Ora Serrata (Figure 2). If a preterm baby is examined a week or so after birth, it is possible to see whether the blood vessels are mature and have reached the Ora Serrata, or whether they are immature; i.e., the peripheral retina is not vascularized. If babies receive good neonatal care, the retinal blood vessels continue to grow normally. If the neonatal environment is not ideal, mainly if oxygen levels have been higher or more variable than they should be, the retinal blood vessels stop growing. A visible line or a ridge then forms, and due to the resulting hypoxia, the blood vessels may start to multiply (proliferate) abnormally. The visible line, ridge, and proliferating blood vessels are all signs of ROP (Figure 3). In 5–10% of premature babies, ROP progresses and can lead to retinal detachment (Figure 4). This causes irreversible blindness, often in both eyes.

Screening

High sensitivity considerations are needed for the screening program for ROP, as this will result in low specificity. Thus a large number of infants need to be screened in a high-risk ROP population to identify the presence of cases with ROP that might result in blindness. Screening, therefore, is costing money; the care for an infant developing blindness, however, is more costly.

Figure 1 In the full-term eye, the retinal blood vessels are fully developed

Figure 2 In the preterm eye, the retinal blood vessels are not fully developed

Figure 3 ROP occurs at the junction between the vascularised and unvascularised retina

Figure 4 Advanced ROP with partial retinal detachment

In defining screening criteria, appropriate limits for birth weight and gestational age must be considered to identify infants at the highest risk of developing ROP.

The screening criteria for ROP differ slightly between countries and between NICUs. In High-Income Countries (HIC), most recommendations state that infants with a birth weight of less than 1250-1500g or a gestational age of less than 30-32 weeks should be screened for ROP. (30-32) Whereas in LMIC recommendations usually include criteria for patients with higher gestational age or higher birth weight (30-32) to avoid missing cases that require ROP treatment if we only rely on the AAP criteria (American Academy of Pediatrics (33) or the Royal College of Pediatrics and Child

Health. (34) The screening criteria must be adjusted to the local situation regarding ROP cases in these countries.

Based on our clinical observations and supported by studies done in LMIC like Indonesia (28,29), we hypothesized that the incidence of Retinopathy of Prematurity (ROP) in Indonesia is higher compared with HIC. If this hypothesis is correct, more infants in Indonesia will develop ROP with all its complications, compared to developed countries. Efforts then are needed to prevent as much as possible the development of ROP in preterm infants in Indonesia. In this thesis, we will look for the actual number of infants with ROP and explore the various risk factors for ROP to overcome these problems, and find the optimal way to reduce the high incidence of ROP. We developed the following questions to answer the above hypothesis.

Questions

1. What is the incidence of ROP in Indonesia?
2. How high is the incidence of ROP in Harapan Kita Women and Children Hospital, which is one of the referral centers for neonatology services in Indonesia?
3. What are the risk factors for ROP in Indonesia?
4. Do genetic factors play a role in the incidence of ROP in Indonesia?
5. What is the root of the problem that arises at various hospital service level settings that greatly influence efforts to reduce the high incidence of ROP?
6. How to reduce the incidence of ROP in Indonesia?

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CHAPTER 2

Retinopathy of prematurity in Indonesia: Incidence and risk factors

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Abstract

Background: Retinopathy of prematurity (ROP) is a vaso-proliferative disease of the eye, which mainly affects preterm newborn infants with an incompletely vascularized retina. The incidence of ROP has increased in industrialized countries due to the increased survival of extremely low birth weight (ELBW) infants. ROP is also increasing in developing countries like Indonesia, where it is most likely due to the improved survival of ELBW infants.

Objective: To ascertain the incidence of ROP and possible risk factors associated with the development of ROP in preterm infants in Indonesia.

Methods: We reviewed the literature on the incidence and potential risk factors for the development of ROP in Indonesia, obtained data from three referral eye clinics and added data from our institution.

Results: The reported incidence of all stages of ROP in infants with a gestational age of <32 weeks ranged from 18-30%. One study showed that ROP also occurred at older gestational ages. Blindness due to ROP was seen in infants up to 35 weeks and with a birth weight of 2000g.

Conclusion: Retinopathy of prematurity is an important cause of ocular morbidity and blindness in Indonesia. The overall incidence of ROP in infants born below 32 weeks in Indonesia is higher than in developed countries, and it is seen in infants with older gestational ages. This might be due to a less strict monitoring during the use of oxygen in Indonesia compared to industrialized countries.

1. Introduction

The introduction of modern technology in neonatal intensive care units (NICU) has resulted in remarkable improvements in the survival of the sickest and most premature newborn infants, including in Indonesia. Although the incidence of disability among NICU graduates has not increased with such advances, the total number of these infants in the community has grown as a result of the improved survival [1]. Many of the surviving infants show complex problems and are at risk for developmental difficulties. One of the severe complications of prematurity is retinopathy of prematurity (ROP). This is a proliferative disorder of the developing retinal vasculature. The spectrum of ophthalmological findings in ROP ranges from minimal sequelae, which do not affect vision, to bilateral retinal detachment and total blindness [2, 3]. ROP is considered an index of overall quality of perinatal and neonatal care. A low incidence of ROP is considered an indicator of a high quality of neonatal care [4].

Retinopathy of prematurity is now emerging as a very important cause of blindness in children in middle-income countries in Latin America and Eastern Europe. This is related to improvements in neonatal intensive care in these countries, characterized by rapidly improving survival of less mature and smaller babies together with a limited control of oxygen delivery (the third epidemic). Retinopathy is also increasingly reported in Asian countries, particularly India and China, where it is likely to become an important cause of blindness in children, as these economies improve and services for the care of premature babies expand without proper monitoring of oxygen delivery [5].

Data on the occurrence of ROP in Indonesia are very limited. A rapid expansion of neonatal units in Indonesia has recently taken place, which has resulted in an increased survival rate for very preterm infants (data from the Department of Health, Indonesia). Given the experience in India and China, this might lead to an increased occurrence of ROP. The aim of this study is to analyze the data on the occurrence of ROP in Indonesia. These data are important in order to set up studies to prevent ROP in Indonesia.

2. Objective

To describe the incidence of ROP and to evaluate the possible risk factors associated with the development of ROP in preterm infants in Indonesia.

3. Methods

To obtain data on the occurrence of ROP in Indonesia, we searched Google and PubMed for papers published between December 1 2003 to December 31 2013 in English and Indonesian. Search words/terms were as follows: newborn, epidemiology, incidence, prevalence, rate, ROP, blindness. We contacted the two eye clinics in Jakarta and the one in Surabaya which are the referral centers for infants with ROP and/or blindness in Indonesia. Data published from these three eye clinics are also reported. We also contacted all members of the National Indonesian Committee on ROP as well as the Heads of all Neonatal Intensive Care units in Indonesia via e-mail/direct calls, and asked whether they were aware of unpublished or ongoing studies. The reference lists of all articles selected were reviewed, and the full texts of potentially interesting studies were examined. The validity and quality of the studies analyzed were evaluated using a checklist based on the MOOSE (Meta-analysis of Observational Studies in Epidemiology). We added the data obtained in our Hospital on ROP cases in the period January 1 2015 to December 31 2013.

4. Results

We identified 11 papers on ROP from Indonesia. We disregarded papers in which overlapping cohorts were described and papers where insufficient data were provided regarding the screening criteria or clinical data of the infants. We were then left with four papers, to which we added data gathered in our hospital between 2005 and 2013. An overview of the results described in these papers is given in Table 1. The incidence of any stage of ROP in infants with a birth weight of <1500 g and/or a gestational age of <32

weeks ranged from 11.9–30.5% [6–9]. One study included all infants born with a birth weight of <2500 g and a gestational age of <37 weeks, with a risk factor, and found an incidence of 26% [6]. The incidence of ROP in the other reports ranged from 12.5%–33.3% [10–12]. The incidence of ROP grade III or higher was 4.8%, 9.6% and 10% in the three studies that reported these data [6, 8, 9], and 3.6% in our own hospital. Risk factors for the development of ROP were asphyxia, blood transfusions, oxygen therapy for more than 7 days, sepsis, PDA, and a gestational age of <28 weeks [6–9]. In our search, we also identified one paper indicating that ROP contributed to 1.1% of all cases of blindness in children in Indonesia [13, 14]. Data reported in 2012–2013 from the Dept. of Ophthalmology FKUI, Harapan Kita Women and Children Hospital, the Undaan Eye Hospital, and the Jakarta Eye Center, the centers in Indonesia where infants with blindness are seen, indicate that severe stages of ROP were found in infants with a gestational age of up to 35 weeks and or a birth weight of up to 2000 g [8, 15]. Yulia et al. collected ROP cases in 2010–2011 from the ophthalmology centers in Jakarta and Surabaya. They found 80 infants with blindness due to ROP. Twelve of these infants (15%) had a birth weight of 1500–1750 g, eight (10%) of 1750–2000 g, and one infant had a weight of >2000 g (1.3%) (Table 2) [15].

In our hospital we found 6 infants born between 2005 and 2013, with a birth weight between 2042–3080 g and GA 34–40 weeks, who developed ROP. Five patients showed grade I-II, and 1 patient grade III. This patient had a birth weight of 2042 g and was born after 40 weeks. All these infants showed respiratory distress and received supplemental oxygen.

Table 1 Data on the prevalence of ROP in Indonesia [6-9]

No	Title	Author - year of publication	Year infants were born	Prevalence	ROP stage/screening criteria	ROP+ / total infants	Risk factor
1	Retinopathy of prematurity: Prevalence and risk factors	Rohiswatno, 2005 (6)	Dec 2003– May 2005 hospital-based	26%	Any degree criteria BW≤2500 g, and or GA≤37 weeks	19/73	Asphyxia, multiple blood transfusions and O2 therapy≥7 days
2	Risk factors for developing retinopathy of prematurity in preterm infants	Prayudijanto A, Siswanto JE, 2009 (7)	2009 hospital-based	30.5%	Any degree criteria BW≤1500 g, GA≤32 weeks + risk factor	10/29	Sepsis, PDA
3	Application of the screening criteria for retinopathy of prematurity in preterm infants in Women and Children's Harapan Kita Hospital, Jakarta	Siswanto JE, Widodo N, Ronoatmojo S, Sauer PJJ (Personal Communication)	2005 – 13 hospital-based	28.8%	Any degree criteria BW≤1500 g, GA≤34 weeks + risk factor	159/553	BW<1500 g
4	Prevalence and risk factors of retinopathy of prematurity	Badriah, 2012 (8)	Jan 2005– August 2010 hospital-based	11.9%	Any degree criteria BW≤1500 g, GA≤32 weeks + risk factor	32/269	BW≤1000 g, O2 therapy≥7 days, and GA≤28 weeks.
5	Screening Retinopathy of Prematurity di Rumah Sakit dengan Fasilitas Terbatas	Rizalya, 2013 (9)	2009 hospital-based	18.3%	Any degree criteria BW≤1500 g, GA<32 weeks + risk factor	11/60	Sex, ventilator, sepsis, blood transfusions

Table 2 Patients with late-stage ROP (stage 4b and 5) treated in the three Indonesian ROP centers in 2010 - 2011^[15]

Gestational age		Birth weight	
<28 weeks	48	<1000 g	15
29–30 weeks	15	1000 - 1500 g	44
31–32 weeks	14	>1500 - 1750 g	12
33–34 weeks	0	>1750 - 2000 g	8
>35 weeks	3	>2000 g	1
Total	80	Total	80

5. Discussion

It is difficult to compare these data on the incidence of ROP in Indonesia with results from developed countries, because infants admitted to an NICU in Indonesia have, on average, a higher birth weight and gestational age compared to industrialized countries. Studies from the USA show an incidence of all stages of ROP, ranging from 40% in infants with a birth weight of 1101–1200 g to 90% in infants of 501–600 g [16, 17]. A correlation was found with gestational age, with an increase from 35% at a gestational age of 31 weeks to 95% at 24 weeks. Data from Sweden (Larsson et al. and EXPRESS study) showed an incidence of all stages of ROP, ranging from 18% (birth weight <1500 g), 34% (birth weight <1000 g), and increasing up to 61% (for babies with a gestational age <27 weeks) [18, 19]. There are, however, important differences between the infants diagnosed with ROP in the USA, Sweden (Europe), and Indonesia. ROP is almost never seen in industrialized countries in infants born after 32 weeks. Second, severe ROP is almost only seen in infants with a birth weight of <750 g and/or gestational age of 24–26 weeks. In Indonesia, ROP is seen in infants with a much higher weight and gestational age.

A recent meta-analysis of retinopathy showed that the incidence of ROP is related to the neonatal mortality in different parts of the world [20]. The estimated median incidence of ROP in infants born <32 weeks in a country with a neonatal mortality rate (NMR) of less than 5 was estimated as 21.8%. In countries with an NMR of >5, this incidence was estimated as 36.5%. The

NMR in Indonesia was 19% in 2013; therefore, these data correlate very well with the incidence of ROP of 18–30% found in this survey. The risk of progression of the disease was also much higher in the countries with a higher NMR: 36.4% vs 18.1% (in Indonesia 33.3–54.5%). The estimated death rate for infants born after a gestational age of <28 weeks in countries with an NMR<5 was 28.3%, compared to 57.7% in countries with an NMR of >5 [21]. Reliable data on the mortality of infants <28 weeks are not available for Indonesia. In our NICU with an NMR 17.8‰ in 2013, the mortality in infants born <28 weeks is 41.7% while in group <32 weeks 17.6%. We can assume that this figure is much higher for the whole of Indonesia, as NICUs are not present in many parts of our country.

The incidence of ROP, as found in this survey, is most likely an underestimation of the real incidence. First, the papers reviewed only included data on the infants who were screened. Second, infants who developed ROP but died before any investigation was done were not included. Third, we only found results from neonatal centers with a good level of expertise and equipment. We did not find data for small, local hospitals, where caregivers are less well trained in the use of oxygen, and where systems to monitor oxygen administration and saturation are often lacking. Finally, the papers we studied did not include the total number of infants <32 weeks cared for in that institution or who died.

Oxygen is considered to be the main inducer of ROP [21]. A number of studies have evaluated the effect of different saturation levels in preterm infants on the incidence of ROP (STOP-ROP, SUPPORTROP, and BOOST II) [22–24]. A saturation level of <92 might reduce the risk of ROP but at the expense of a higher mortality rate. Based on the partly conflicting results of these studies, it is now advised to set saturation limits at 90–95% [2]. This poses a problem for developing countries like Indonesia, where saturation monitors are not widely available. Without these monitors, it is impossible to titrate the use of oxygen to obtain these levels. It might be unavoidable, therefore, that small preterm infants will be subjected to higher oxygen levels in order to keep them alive, with ROP as a result. This is also a major

factor for infants up to 36 weeks, as our data show that oxygen is also dangerous for these infants.

The studies conducted in Indonesia found partly the same and partly different risk factors for the development of ROP, compared to studies in developed countries. From the Indonesian studies, we identified a lower birth weight and gestational age, asphyxia, multiple blood transfusions, administration of oxygen for more than 7 days, oxygen concentration in inspired air, ventilator use, PDA, and sepsis/septicemia as risk factors. All these factors indicate that the most immature and sick infants have the highest risk of developing ROP; however, it also develops in less sick or preterm infants with good lungs, when supplemental oxygen is given. In nurseries with more limited human and equipment resources, inadequate neonatal care is likely the major contributor to the development of ROP [25]. This explains why ROP in Indonesia is not, as in developed countries, a disease found mainly in very immature infants born after 23–26 weeks. It also explains why infants born at higher gestational ages, who received supplemental oxygen, develop ROP and need to be screened in Indonesia. The real incidence of ROP in infants born >32 weeks in Indonesia is not known and might well be higher than we found. It is not common practice to screen infants >32 weeks for the development of ROP, nor when they have received supplemental oxygen.

A study from a school for blind children in Indonesia showed that, in 1.1% of the registered infants, ROP was the cause of their blindness [13]. This is in line with other studies of children in schools for blind children in China, India, and Sri Lanka [26–29]. In a school in South Africa, 10.6% of the blindness was due to ROP, but only 1.25% of these children were from the black population [28]. Studies from developed countries showed a much higher percentage of children who were blind due to ROP in these schools. Most likely this is due to a higher number of children with some other preventable cause of blindness in emerging compared to developed countries [29].

An increasing number of hospitals in Indonesia are presently taking care of preterm infants with lower and lower birth weights. This is a very positive

trend that will help to increase the survival rate of these infants. At the same time, however, and especially when equipment to monitor the use of supplemental oxygen is lacking, this development may be dangerous. It may cause an increase in the rate of infants with ROP.

Achieving a lower incidence of prematurity through better antenatal and obstetric care is needed in Indonesia. The use of antenatal corticosteroids, when preterm birth is inevitable, needs to be stimulated. Some components of good neonatal care can be introduced even in resource-poor situations. These include good temperature control with the avoidance of hypothermia, decreasing unpleasant or unnecessary handling, and the use of analgesia for painful procedures. In addition, measures to decrease infection rates, improve growth, and encourage breast-feeding are components of good neonatal care. Most important of all, however, are the control of oxygen administration and the monitoring of oxygen saturations for babies receiving supplemental oxygen in developing countries.

6. Conclusion

ROP is a threat to the vision of babies in areas of the world where increasing numbers of premature babies are surviving due to the introduction of neonatal care. At the present time, the incidence of ROP in NICU centers in Indonesia is higher than in developed countries. It is very important that, in all infants receiving supplemental oxygen, saturation in the blood is monitored as well as the concentration of oxygen administered. Awareness of the possibility of this blinding disease needs to be augmented among medical and nursing staff taking care of preterm infants.

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CHAPTER 3

Eleven years of retinopathy of prematurity in one neonatal intensive care unit in Jakarta, Indonesia

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2. Pediatric Academic Societies 2017 Meeting, the Moscone Center, San Francisco, California, May 6-9, 2017 on the topic: Eleven years of Retinopathy of Prematurity in one NICU in Jakarta, Indonesia.
3. BIT's 5th International Congress of Gynaecology and Obstetrics China, November 1-3, 2017 on the topic: Sustainability analysis over 10 years experience of Retinopathy of Prematurity screening program in Indonesia; Hospital based data (2005-2015).

Abstract

Background Retinopathy of prematurity (ROP) is a well-known complication in preterm infants. Data on the incidence of ROP in Indonesia, in relation to birth weight (BW) and gestational age (GA), are limited.

Objective To report the incidence of ROP in one of the oldest and largest neonatal intensive care unit (NICU) in Indonesia.

Methods We studied the incidence and severity of ROP in inborn infants with a BW of ≤ 1500 g and/or GA of ≤ 32 weeks, who were admitted to the NICU of Harapan Kita Women and Children Hospital, Jakarta. In addition, infants with a higher BW and GA, receiving more than 40% oxygen for a longer period, were screened.

Results In 2005–2015, 182 infants were born with a BW of <1000 g and 437 with a weight of 1000–1500 g. In the <1000 g group, 27 (46%) of the screened infants showed no ROP, 22 (37%) showed ROP 1–2 and 10 (17%) showed ROP 3–5. In the 1000–1500 g group, 172 (68%) were without ROP, 71 (28%) with ROP 1–2 and nine (4%) with ROP 3–5. Twenty-two (13%) of the 163 screened infants weighing 1500–2000 g showed ROP 1–2 and two (1.2%) had ROP 3–5. Eight (18%) of the 44 screened infants born with a BW of more than 2000 g showed ROP 1–2 and none showed ROP 3–5.

Conclusion The total incidence of ROP as well as severe ROP in infants with a BW of <1000 g and 1000–1500 g in our NICU is higher than in a developed country. ROP in Indonesia is also seen in infants with a BW of 1500–2500 g. Increasing the awareness of the risks of oxygen as well as better equipment to monitor oxygen delivery is essential.

Introduction

Retinopathy of prematurity (ROP) is a vision-threatening disease occurring in preterm infants related to an abnormal retinal vascular development. The disease can both regress and progress into blindness. The role of oxygen in the development of the disease is undisputed.¹ The main risk factors for the development of this condition are gestational age (GA) and birth weight (BW).¹ In developed countries, ROP is mainly seen in infants born after a GA of less than 28 weeks with a range of 16%–33%.¹

The survival of preterm infants in low-income and middle-income countries has increased due to the introduction of neonatal intensive care centres. A relatively high rate of ROP is seen in both preterm survivors and in infants at higher GA.^{2–4}

Indonesia is a country with a very rapid expansion of neonatal intensive care centres while facing financial limitations at the same time. One of the first neonatal intensive care units (NICUs) in Indonesia was founded in 1986 at Harapan Kita Hospital, Jakarta, with a capacity of 14–20 beds. We examined the incidence of ROP in the period of 2005–2015 in infants treated in this hospital to identify what could potentially occur in Indonesia after wide spread introduction of neonatal intensive care.

Methods

All preterm infants with GA of ≤ 32 weeks and birth weight (BW) of less than 1500 g, admitted to the NICU of Harapan Kita Women and Children Hospital Jakarta Indonesia, in January 2005–December 2015 were included. According to the hospital's policy, these infants were screened for ROP. We also included infants with a higher GA when screening for ROP, as our policy also require us to perform ROP screening in infants with GA higher than 32 weeks and BW higher than 1500 g, when these infants are hemodynamically unstable and/or ventilated with more than 40% oxygen. GA was based on the mother's last menstrual period or the result of an ultrasound made during pregnancy. All infants were scored clinically using Ballard score. A

single ophthalmologist performed all eye examinations using indirect ophthalmoscopy and scleral depression. Retcam examination was performed in a few patients to evaluate the progression of ROP. Indirect ophthalmoscopy was performed using 28 diopter lens. Mydriatic eye-drops were administered 30 min before examination. Time of first eye examination and follow-up examination was determined according to American Academic of Pediatrics (AAP) guidelines.⁵ Follow-up examinations were recommended by the ophthalmologist according to recommendations from the International Committee for the Classification of Retinopathy of Prematurity.⁶ All infants were followed-up until a stable retinal situation was reached. Informed consent was obtained from all parents.

Results

In this 11-year period, 182 inborn infants with a BW of <1000 g and 437 infants with a BW of 1000–1500 g were admitted to our NICU. One hundred and eighty-five infants were born before 28 weeks and 569 between 28 and 32 weeks (table 1). In the <1000 g group, 27 (46%) infants had no ROP, 22 (37%) had ROP 1–2 and 10 (17%) had ROP 3–5. In the 1000–1500 g group, 172 (68%) infants had no ROP, 71 (28%) had ROP 1–2 and nine (4%) had ROP 3–5. Annual incidence data are shown in table 2a, b.

Table 1 Clinical characteristics and the incidence of ROP of inborn infants admitted to neonatal intensive care unit in Harapan Kita Women and Children Hospital, 2005–2015

BW (g)/GA (wks)	<1000 g	1000–1500 g	>1500–2000 g	>2000 g	<28 weeks	28–32 weeks	>32–34 weeks	>34 weeks
n (inborn)	182	437	748	1618	185	569	NA	NA
GA (weeks)	26–32	26–35	29–34	32–40				
BW (g)					529–1200	676–2100	700–2270	1100–3175
Died	85	72	–	–	91	126	–	–
Screened	59	252	163	44	47	261	156	107
Screened/survived (%)	61%	69%	–	–	48%	59%	–	–
ROP (–)	27	172	139	36	28	187	126	91
ROP 1–2	22	71	22	8	9	66	29	13
ROP 3–5	10	9	2	0	10	8	1	3
Prevalence of any ROP (%)	54%	32%	15%	18%	40%	29%	19%	15%
Prevalence of severe ROP (%)	17%	4%	1%	0%	21%	3%	1%	3%

n (inborn) GA >32 to ≤34 weeks and >34 weeks not available.

BW, birth weight; GA, gestational age; ROP, retinopathy of prematurity.

Table 2 Annual incidence of ROP in infants admitted to neonatal intensive care unit in Harapan Kita Women and Children Hospital, 2005–2015

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	Percentage
(a) BW of <1000 g													
Admitted	13	20	15	12	13	8	15	12	24	21	29	182	
Died	4	9	5	7	6	5	2	5	13	13	16	85	47%
Screened	2	7	2	5	3	3	5	4	11	8	9	59	61%
ROP (–)	1	3	1	3	0	1	2	1	5	4	6	27	46%
ROP 1–2	0	2	0	2	3	2	1	2	5	3	2	22	37%
ROP 3–5	1	2	1	0	0	0	2	1	1	1	1	10	17%
(b) BW of 1000–1500 g													
Admitted	37	31	32	22	44	33	27	33	50	47	81	437	
Died	14	5	1	3	9	3	6	4	3	10	14	72	16%
Screened	10	14	17	16	32	22	21	16	23	37	44	252	69%
ROP (–)	5	12	14	12	20	17	9	13	11	20	39	172	68%
ROP 1–2	5	1	3	4	11	2	12	3	11	14	5	71	28%
ROP 3–5	0	1	0	0	1	3	0	0	1	3	0	9	4%

BW, birth weight; ROP, retinopathy of prematurity.

Of the infants born <28 weeks, 28 (60%) had no ROP, nine (19%) had ROP 1–2 and 10 (21%) had ROP 3–5. Of the infants born after 28–32 weeks, 187 (72%) showed no ROP, 66 (25%) showed ROP 1–2 and eight (3%) showed ROP 3–5. The number of admitted infants in both groups increased over time, while the mortality showed a decrease (figure 1). The percentage of infants with severe ROP seemed to decrease over time (table 3a, b).

Figure 1 Mortality of infants born after <28 and 28–32 weeks in neonatal intensive care unit in Harapan Kita Women and Children Hospital, Indonesia, 2005–2015.

Table 3 Annual incidence of ROP in infants admitted to neonatal intensive care unit in Harapan Kita Women and Children Hospital, 2005–2015

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	Percentage
(a) Born at GA of <28 weeks													
Admitted	12	12	22	18	15	9	11	15	10	21	40	185	
Died	10	8	12	11	9	5	5	9	4	8	6	87	47%
Screened	2	4	3	2	2	4	3	5	6	6	10	47	48%
ROP (–)	1	2	1	1	0	2	2	3	5	4	7	28	60%
ROP 1–2	0	0	1	1	1	2	0	1	0	1	2	9	19%
ROP 3–5	1	2	1	0	1	0	1	1	1	1	1	10	21%
(b) Born at GA between 28 and 32 weeks													
Admitted	32	38	50	45	51	44	30	55	60	65	99	569	
Died	12	12	15	16	13	7	5	10	6	17	13	126	22%
Screened	13	22	20	9	27	26	27	16	21	36	44	261	59%
ROP (–)	9	18	19	7	17	20	15	12	10	22	38	187	72%
ROP 1–2	4	3	1	2	9	3	11	4	10	13	6	66	25%
ROP 3–5	0	1	0	0	1	3	1	0	1	1	0	8	3%

BW, birth weight; ROP, retinopathy of prematurity.

In this 11 years' period, 156 infants born between 32 and 34 weeks and 107 born after 34 weeks were screened for ROP. Twenty-nine of the infants born between 32 and 34 weeks showed ROP 1–2 and one infant had ROP 3–5. Thirteen of the infants born after 34 weeks showed ROP 1–2 and three infants showed ROP 3–5.

Discussion

When we compare the incidence of ROP during the last 3 years in our NICU with data from developed countries, we see that the incidence in our unit is higher compared with that in developed countries. Forty per cent of infants with a GA of <28 weeks had ROP of all stages and 21% showed ROP>3. More concerning is the incidence of ROP in our patients with a GA of 28–32 weeks where any stage ROP was found in 29%, and ROP>3 in 3% of the screened infants. Finally, ROP was also observed in infants with a GA of >32 weeks or a BW of >1500 g.

The incidence of ROP in our unit is comparable with data from other developing countries, as presented recently in a review by Zin and Gole.² Severe ROP was found in infants with a BW of <1500 g and/or a GA of <32 weeks ranging from 20.6% in Pakistan to 5.9% in Brazil. Our data showed

that 6% of all screened infants of BW below 1500 g and/or a GA of ≤ 32 weeks fit well in this range. Blencowe et al estimated the incidence of all stage of ROP in infants < 32 weeks in developing countries as 36.5%.³ The incidence, however, is very dependent on both the infant mortality rate (IMR) and neonatal mortality rate (NMR) in each country and the mortality in the NICU. The IMR is a reflection of the level of access to and the quality of healthcare and the level of socioeconomic development. The higher the IMR and NMR, the higher the incidence of ROP. The higher neonatal mortality might also cause underestimation of the incidence of ROP. The mortality rate of infants < 32 weeks admitted to our NICU in the past few years is not much higher compared with developed countries. The incidence of ROP is higher. Our data on the incidence of ROP might be an underestimation of the real incidence of ROP given the higher mortality in our total cohort.

It is not clear which factor might be responsible for the higher incidence of severe ROP in developing countries like Indonesia compared with developed countries. Gilbert reported a correlation between the incidence of ROP and the IMR,⁷ indicating that a lack of resources might be involved. The most likely explanation for the higher incidence of ROP in our NICU is a less strict control of oxygen delivery.

One limitation of this study is the relatively small size of infants subjects studied. However, our unit is one of the largest NICUs in Indonesia. Combining data from different centres with potentially different modes of ROP screening also would not increase the reliability of the data. Therefore, we present only the data obtained in our centre, which might be representative of the current situation in our country. Another limitation is that not all infants were screened. When the one ophthalmologist who did all the screening was not available, no other experienced ophthalmologist could conduct the screening. Second, not all infants in the first period of the study were screened; a strict protocol was introduced in 2009. Finally, some infants were considered too unstable to investigate. We do not believe that the missing infants caused a bias in the results.

Conclusion

The incidence of ROP in infants with a GA of <28 weeks and 28–32 weeks and a BW of <1000 g and 1000–1500 g in our NICU is higher than in developed countries. A higher incidence of severe ROP was also observed. ROP was also seen in infants with a BW of 1500–2500 g born at a GA of >32 weeks. A stricter control of oxygen delivery in preterm infants in Indonesia is needed to reduce the incidence of ROP. Increasing the awareness of oxygen as well as better equipment to monitor oxygen delivery in Indonesia is essential.

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CHAPTER 4

Risk factors for the development and progression of retinopathy of prematurity in preterm infants in Indonesia

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Abstract

Background: Risk factors other than supplemental oxygen might play a role in the development of retinopathy of prematurity (ROP). In Indonesia ROP occurs in infants up to 34 weeks and 2000 g. Risk factors for the development of ROP in Indonesian NICUs have not been evaluated. Our aim was to identify other risk factors than the use of oxygen in the development and progression of ROP in preterm infants in Indonesia.

Methodology: Ninety-eight preterm infants with ROP and 77 controls were collected from four NICUs and two eye centers in Jakarta, Indonesia, between 2009 and 2014. We used multivariate logistic regression analysis to determine the relationship between infants and environmental variables and the development and progression of ROP. We obtained variables for ROP severity by using Cox regression analysis.

Results: Factors associated with the development of ROP were birthweight, intrauterine growth retardation (IUGR), exchange transfusion, duration of oxygen supplementation, minimum saturation monitor setting, and socioeconomic factors. Regarding the progression, gestational age (GA), out-born, duration of supplemental oxygen, minimum saturation monitor setting, and socioeconomic factors were identified as risk factors.

Conclusion: The use and control of supplemental oxygen are the main risk factors for the development and progression of ROP in preterms in Indonesia. Additionally, we confirm that GA, birthweight, and IUGR are risk factors. Moreover, we found exchange transfusion to be a risk factor, and we found a lower rate of ROP in infants from a lower socioeconomic background. These risk factors apply to infants with a GA up to 34 weeks and a birthweight up to 2000 g.

Introduction

Over the past few years the number of NICUs and the possibility to treat sick newborn infants has increased significantly in Indonesia. With the introduction of intensive care, the survival rate of very preterm infants increased. However, more survivors might also mean an increase in infants with handicaps related to preterm birth and complications arising during treatment. An important complication of very preterm birth is the development of retinopathy of prematurity (ROP). At Harapan Kita Hospital Jakarta, Indonesia we found that 40% of infants born before 28 weeks and 29% of infants born after 28 to 32 weeks developed ROP [1]. In Indonesia the incidence of ROP is higher than in developed countries where ROP is seen mainly in infants born before 28 weeks and hardly in infants with a higher gestational age (GA) [2]. We found that in Indonesia ROP is also seen in late preterm infants [2]. In developed countries the development of ROP is strongly related to GA at birth, birthweight, and the use of supplemental oxygen [3]. Other factors such as surgical intervention during the neonatal period also influence the risk of developing this disease [3]. To date, no study evaluated which risk factors might play a role in the development of ROP in NICUs in Indonesia. This information is indispensable in the effort to reduce the incidence of ROP in developing countries such as Indonesia.

The aim of this study was to identify whether in Indonesia risk factors other than the use of oxygen contribute to the development of Type 2 and the progression to Type 1 ROP.

Methods

We included all infants admitted to four NICUs in Jakarta, Indonesia, RSAB Harapan Kita, RSIA Budi Kemuliaan, RS Awal Bros Tangerang, and RS Royal Taruma, who were diagnosed with Types 1 and 2 ROP and infants with ROP who were referred to the Jakarta Eye Centers Kebon Jeruk and Menteng. The criteria for treating ROP were based on the Guidelines for Early Treatment for Retinopathy of Prematurity (ETROP). These guidelines were

used to identify infants at high risk of adverse outcomes due to ROP. Type 2 ROP signifies ROP not severe enough to require treatment and Type 1 ROP is defined as ROP that does require treatment [4]. Preterm infants without ROP and who were cared for in the same hospitals served as controls. We considered 27 risk factors, including GA, birthweight, IUGR, diseases like respiratory distress syndrome, asphyxia, apnea, sepsis, patent ductus arteriosus, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH), the use of oxygen, the setting of the saturation monitor, and diseases of the mother like preeclampsia. The full list of factors we evaluated is given in Table 1. We included the socioeconomic status of the mother because access to medical care is limited in the Indonesian population with a lower socioeconomic background.

Statistical methods

We conducted a clinical study using an epidemiologic approach consisting of two steps. Step I: case control study to evaluate the factors of neonatal management associated with the development of ROP. Step II: using a combination of retrospective and prospective cohort design to evaluate risk factors related to the progression of ROP. In this design exposures are the neonatal risk factors and outcomes are the progression of ROP (Type 1 or Type 2).

Data analysis started with a univariate analysis to determine the patterns and characteristics of the variables, after which the crude odds ratio (COR) was obtained with a bivariate analysis to evaluate the association between potential risk factors and ROP. Subsequently, a multivariate analysis was carried out by logistic regression analysis to obtain the adjusted odds ratio (AOR) and its relation with the development of ROP. This was achieved by compiling all the independent variables with $P < .25$ in the bivariate analysis into multivariate models. Prediction of ROP severity was made with logistic regression, where its variable is obtained from the Cox proportional hazards regression procedure.

Cox regression is a procedure that uses a multivariate approach to investigate the effect of several predictor variables on the time it takes for a

specified event to occur. This analysis describes the relation between event incidence, as expressed by the hazard function and a set of covariates. We use a hazard ratio to obtain the risk ratio. The hazard ratio resulting from the Cox regression analysis is frequently interpreted as the risk ratio or the relative risk. The difference between the two is that the risk ratio does not take the timing of the event into account but only considers the occurrence of the event at the end of the study period. In this study the outcome of Types 1 or 2 ROP was monitored until 44 weeks' PMA.

We created two different models for the development and progression of ROP: Model 1 is a development and severity model based on variables of oxygen exposure that can be intervened (FiO_2), types of oxygen supplementation, and duration of oxygen supplementation. Model 2 is a development and severity model based on variables that appraise SpO_2 . We created these models because the oxygen exposure variables we put into Model 1 could change the results of SpO_2 (Model 2). Co-linearity existed in the multivariate analysis when the SpO_2 variable (in Model 2) was placed in one table with the oxygen exposure variables present in Model 1, so we decided to analyze the role of each variable in the two different models.

Results

One hundred and seventy-five infants were included in the study: 98 patients suffered ROP and there were 77 controls. Thirty-seven infants had Type 1 ROP (38%) and 61 infants had Type 2 ROP (62%). The clinical characteristics of the infants are shown in Table 2. Eleven out of thirty-seven (32%) infants with Type 1 ROP had a GA of less than 28 weeks compared to 3 of 61 (5%) infants with Type 2 ROP ($P < .001$). We found the same trend for birthweight, in which case 13 out of 37 (35%) infants with Type 1 ROP had a birthweight of less than 1000 g, as compared to 11 of 61 (18%) in the Type 2 ROP group. There were no significant differences between the infants with Types 1 and 2 ROP regarding IUGR and sex (Table 2). We also did not find significant differences between infants with ROP and controls regarding GA,

IUGR, and sex. Birthweight was significantly lower in the group that developed ROP (Table 2).

The risk factors we found for the development of ROP when using Model 1, based on the oxygen variables that can be intervened by a clinician, were IUGR, exchange transfusion, a duration of oxygen exposure of more than 16 days, minimum saturation monitor setting, and socioeconomic factors (Table 3). According to Model 2 for identifying risk factors based on the variables that appraise SpO₂ we found birthweight, exchange transfusion, minimum saturation monitor setting, and socioeconomic status to be risk factors (Table 3).

When using Model 1 for the progression of ROP, the risk factors we found included the duration of supplemental oxygen and socioeconomic status (Table 4). Using Model 2, the risk factors significantly associated with the progression of ROP were GA, hospital out-versus in-born, and minimum saturation monitor setting. (Table 4).

Based on our data we calculated that the OR to develop ROP increased by 1.54 when oxygen was given for more than four days, by 2.4 when oxygen was given for five up to 15 days, and by 5.3 when oxygen was given for more than 16 days, as compared to no supplemental oxygen. Infants receiving oxygen for more than seven days had a 4.2 higher risk of developing Type 1 ROP. Infants where the minimum setting of the saturation monitor was 93% or higher, had a 2.8 higher risk of developing Type 1 ROP, as compared to infants where the saturation was set at 85% or less. The risk to progress to Type 1 ROP was higher in out- born compared to in- born infants (Table 4). Out-born infants were more frequently exposed to 100% oxygen and less to blended air and room air.

The treatment modalities of infants with severe ROP were not recorded properly in our data. In nearly half of the infants with severe ROP treatment involved laser photocoagulation and/or intravitreal bevacizumab (IVB) injections. Based on information from our ophthalmologists three infants received IVB therapy, one infant received a combination of IVB therapy and photocoagulation, seven out-born infants received no intervention because

at the time of the first examination they were diagnosed with Periventricular Leukomalacia Grades IV and V. In one infant the parents refused intervention. The majority of the remaining infants received laser photocoagulation therapy.

Discussion

In this study we found that birthweight, IUGR, exchange transfusion, duration of oxygen supplementation, the setting of the oxygen saturation monitor, and socioeconomic factors were related to the development of Type 2 ROP. The progression to severe ROP was related to GA, place of birth, duration of supplemental O₂, the setting of the oxygen saturation monitor, and socioeconomic factors.

A number of studies reported on risk factors for the development of ROP. Recently, Owen and colleagues performed a retrospective cohort analysis of preterm infants referred for ROP screening [3]. They found that GA, birthweight, the need for surgery of whatever nature, and maternal magnesium prophylaxis were related to the development of ROP, irrespective of the stage of the disease. Development of severe ROP was related to GA, the need for surgery of whatever nature, and severe or moderate bronchopulmonary dysplasia at 7 days. In 2013 Hellström and colleagues published a comprehensive review on the development and risk factors for ROP [5]. They identified the use of oxygen, neonatal hyperglycemia, low levels of insulin-like growth factor, insufficient nutrition, absence of n-3 long-chain fatty acids, and late onset sepsis as risk factors for ROP. Many studies demonstrated the relation between the setting of the oxygen saturation monitor and the development of ROP [6]. Setting the monitor at low levels (85%-89%) was related to a lower incidence of ROP, but an increased death rate [7,8]. At the same time, setting the monitor between 90%-95% might increase the incidence of ROP [9]. A recent Cochrane Review of five trials including 4 965 infants <28 weeks' GA targeting the lower levels of SpO₂ compared to the higher levels of SpO₂ found no significant effect on the composite outcome of death or major

disability nor on major disability alone, including blindness. There was, however, an increased average risk of mortality of 28 per 1000 infants treated [8,10].

The oxygen tension, or the substitute the oxygen saturation, is related to the incidence and development of ROP. The SpO₂ monitoring, therefore, is correlated with the incidence and severity of ROP. The SpO₂ monitoring has two monitor settings, the maximum and minimum saturation monitor setting. In this study, we recorded the minimum, mean SpO₂, and maximum oxygen saturation in each sample, both in the cases and controls groups. All three components of SpO₂ are important. When the maximum saturation monitor setting is 95% and the minimum saturation monitor setting 92%, will the mean SpO₂ of the infant be higher than when the minimum saturation monitor setting is 85%. The mean SpO₂ when the saturation monitor is set 95– 92% will be at in between these values. In case the range is between 95%-85%, will the resulting saturation be around 90%. In Indonesia, the maximum saturation monitor is almost always set at 95-100%. The SpO₂ in the infant in Indonesia is, therefore, more dependent on the minimum saturation monitor setting, not the maximum saturation monitor setting. This explains why we did not find a correlation between the maximum saturation monitor setting and the incidence of ROP. We found however that the minimum saturation monitor setting was positively correlated with the incidence of ROP, the higher the minimum saturation monitor setting, the higher the incidence and progression of ROP.

Our results are in line with other studies on the risk factors for ROP in low income and developing countries. Bas and colleagues [11] conducted a prospective, multicenter study in 69 neonatal intensive care units in Turkey. They also found ROP in infants with a higher birthweight and GA. This study showed that red blood cell (RBC) transfusions increased the risks of developing ROP. Transfusions may increase oxygen delivery to the retina because of the lower oxygen affinity of adult hemoglobin in packed red cells. Repeated transfusions may also cause free iron accumulation, which may result in increased production of free hydroxyl radicals, resulting in damage to the retina [12]. We found that the risk of developing ROP was higher in

infants who had received two or more transfusions, but this finding was not statistically significant (COR 1.53 (95% CI, 0.70-3.32, $P > .05$). Most likely our finding that exchange transfusion is a risk for developing ROP has the same explanation as RBC transfusions. In 1997 and 2001, respectively, Hesse and colleagues and Dani and colleagues described a correlation between the occurrence of ROP, iron load, and blood transfusions [13,14]. In 1995, Teoh and colleagues found a correlation between an exchange transfusion and ROP [15]. That we identified exchange transfusion as a risk factor might be related to the more frequent use of exchange transfusions in Indonesia as compared to developed countries. This is due to a relatively high incidence of severe hyperbilirubinemia in Indonesia [16].

More studies from low and middle-income countries found severe ROP in larger preterm infants [17-21]. The use of 100% oxygen as well as insufficient neonatal care [18,20,22], IVH [21], RDS, sepsis, neonatal jaundice, and oxygen therapy [18] might contribute to the development of severe ROP in larger preterm infants. A number of studies, summarized by Lee, found that sepsis and late onset sepsis in particular might be a risk factor for the development of ROP [23]. We found a small but not significant lower incidence of either proven or suspected sepsis in the control infants (57%) compared to ROP patients (65%). Perhaps our cohorts were too small to detect sepsis as a risk factor. We found that the duration of supplemental O₂ and oxygen saturation (SpO₂ $\geq$ 93.5%) in the minimum saturation monitor setting were the most important factors related to the progression of ROP.

The incidence of ROP is higher in Indonesia as compared to developed countries [2]. ROP is also seen at higher GAs. Despite these differences we found that risk factors for the development of ROP are almost equal to the risk factors found in developed countries. Birthweight, GA, duration of oxygen supplementation, and the setting of the saturation monitor were significant in the development and progression of ROP. We found that socioeconomic factors were also related to the development of ROP. The risk of infants born to mothers with a lower socioeconomic status to develop ROP is less. Most likely this is related to the finding that oxygen saturation below 89% decreases the incidence of ROP. Infants born to mothers with a

lower socioeconomic status are at greater risk of being born in an environment where supplemental oxygen is not readily available. Lower oxygen levels in plasma might lead to a lower chance of survival but, at the same time, in surviving infants it might lead to a lower risk of developing ROP [7]. If oxygen is readily available, its misuse might induce the development of ROP.

Our data stress that ROP is not a disease seen only in very preterm infants. ROP also occurs in infants with a GA up to 34 weeks, which is in accordance to the first descriptions of the disease. In 1952, Silverman and colleagues first described retrolental fibroplasia, which was later named ROP, and found that the incidence of retrolental fibroplasia was highest in infants with a birthweight of less than 1 250 g, but that the disease also occurred in infants with a birthweight up to 2 250 g. In this paper the authors described the cohorts of two hospitals in New York. In one hospital the progression to blindness was only seen in infants up to 1 500 g, while in the other hospital progression was also seen in infants up to 2 000 g [24]. Strict control of the use of oxygen should therefore, not be limited to very preterm infants, but to all preterm infants.

Regarding limitations of this study we mention that we did not evaluate the relation between partial pressure of oxygen (PaO_2) and ROP. In clinical practice it is difficult to measure PaO_2 , but it can be estimated from SpO_2 values on the basis that multivariate analyses show that variables of PaO_2 and SpO_2 are collinear. However, there is no good correlation between SpO_2 and PaO_2 above a SpO_2 of 95. A second limitation of our study was that in Step 2 of the research (a combination of retrospective and prospective cohort design) the ROP cases included are the patients who developed ROP (ROP positive) from Step 1 of the case control study, resulting therefore in a larger proportion of Type 1 ROP than what it is supposed to be in the population.

Conclusion

In Indonesia, similar to developed countries, the duration of supplemental O₂ as well as the minimum saturation monitor setting are important risk factors for the development and progression of ROP. We confirmed that GA, birthweight, and IUGR are additional risk factors. Furthermore, we found that exchange transfusion is also a risk factor, while a lower incidence of ROP was found in infants born to mothers with a lower socioeconomic status. These risk factors are also relevant for infants with a GA up to 34 weeks and a birth weight up to 2 000 g.

Increasing awareness of the above factors is needed in Indonesia and other developing countries to reduce the incidence of ROP to levels found in developed countries.

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CHAPTER 5

Norrie disease gene polymorphism in Indonesian infants with retinopathy of prematurity

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2. 10th Malaysia-Indonesia-Brunei Medical Science Conference, UKM (Universiti Kebangsaan Malaysia) Medical Centre, Kuala Lumpur July 26th-28th 2017 on the topic: NDP (Norrie Disease Pseudoglioma) gene polymorphism in Indonesian infants with retinopathy of prematurity. An epidemiology study.

Abstract

Objective Retinopathy of prematurity (ROP) is a major cause of blindness in newborn infants, which also occurs in low-income and middle-income countries. Why ROP progresses in some infants while it regresses in others is still presently unknown. Studies suggest that genetic factors might be involved. Mutations in the Norrie disease (ND) gene are suspected to be related to advanced ROP development. Indonesia is a country with relatively high incidence of ROP, yet the role of these genetic factors in the pathogenesis of ROP cases is still unknown. The study aimed to investigate the presence of mutations in ND on the X chromosome in infants with both non-advanced and advanced ROP in Indonesia.

Methods and Analysis This is a case–control study of polymorphisms in six variants within the ND gene in exon 3, C597A, L108P, R121W, A105T, V60E and C110G, in preterm newborn infants in four major hospitals in Greater Jakarta, Indonesia.

Results We included 162 preterm newborn infants. ROP was diagnosed in 83 infants, and 79 infants served as controls. Among those with ROP, 57 infants had type 2, while others had type 1. We did not find any gene polymorphisms in any of the infants with ROP nor in the control group.

Conclusion We conclude that it is very unlikely that the six polymorphisms in exon 3 of the ND gene studied in this paper are involved in the development or progression of ROP in preterm infants in our population sample in Indonesia.

Introduction

Retinopathy of prematurity (ROP) is a major cause of blindness in preterm infants. The ROP incidence in infants with gestational ages of more than 26 weeks has been decreasing in developed countries due to improved quality of neonatal care. In contrast, an incidence is seen in infants born before 26 weeks.^{1,2} We showed that the incidence of ROP is higher in preterm infants born in Indonesia as compared with developed countries, and is also seen in infants with gestational ages of up to 34 weeks.³ Our results are in accordance with other studies in low-income and middle-income countries.⁴

ROP is a multifactorial disease. Gestational age, birth weight and use of supplemental oxygen are known risk factors. In Indonesia, we found that other factors such as sepsis, asphyxia, patent ductus arteriosus and multiple blood transfusions might also play a role.³ However, none of the presently identified risk factors can explain why some infants develop ROP while others do not. It is also not known why ROP regresses in most of the infants and progresses to severe forms in others.

A number of studies have suggested that genetic factors influence the development and severity of ROP.^{5–14} A study of monozygotic and dizygotic twins showed that genetic factors accounted for 70% of the variance in liability for ROP.⁵ Cooke et al¹³ found that a mutation in the VEGF gene was related to the progression of ROP to threshold levels. Preterm infants who were homozygous for six alleles in the VEGF gene were twice as likely to develop threshold ROP.¹³ Mohamed et al.¹⁴ studied the genetic polymorphisms with candidate genes and genes previously genotyped for associations with preterm delivery. They found that IHH, AGTR1, TBX5, CETP and GP1BA were all associated with the development of ROP.¹⁴ Most studies described an association of mutations in the Norrie disease (ND) gene on the X chromosome with the progression of ROP.^{6–12} However, other studies could not confirm these results. ND, familial exudative vitreoretinopathy (FEVR) and ROP are retinal diseases which share similar phenotypes. ND is caused by a mutation in the Norrie (ND) gene, a condition which leads to a

deficiency of Norrie protein.¹⁵ FEVR is characterized by reduced retinal vascularisation, retinal retraction and retinal detachment.

There are indications that racial differences exist in the development of ROP. Studies have shown a lower incidence of ROP in African–American infants and a higher incidence in Asian infants.¹⁶ That race might be involved in the development and progression of ROP was also found in studies in different populations in the USA.¹⁷

No study has evaluated if the higher number of ROP incidence in Indonesia might be related to the presence of mutations in the ND gene. Therefore, we investigated if mutations in the ND are present in infants with ROP in Indonesia.

Methods

This is a case–control study conducted in four hospitals (Harapan Kita Women and Children Hospital, Budi Kemuliaan Hospital, Awal Bros Tangerang Hospital, Royal Taruma Hospital) in Greater Jakarta, Indonesia. All infants admitted to the neonatal intensive care unit of each hospital and screened for ROP were included in the study. Most patients came from Jakarta, and the rest from West Java, Central Java, Sumatra and Kalimantan. Infants with birth weight less than 1500 g and/or gestational age of less than 32 weeks, and infants with a higher birth weight and/or gestational ages who needed respiratory support, were screened for ROP and included in this study.

Infants diagnosed with ROP type 2 or type 1, according to the Early Treatment for Retinopathy of Prematurity criteria,¹⁸ were included as patients, while infants without ROP were included as controls. A venous blood sample or a buccal swab was obtained from each infant.

DNA Analysis

The basis of this study were Haider et al's¹⁹ findings in 2002 that the incidence of AA genotype of the C597A polymorphism in the ND gene was

considerably higher in advanced-stage ROP cases. Therefore six alterations of the ND gene were analysed by amplifying the ND gene in the third exon using primers from these previous studies.^{7 19} We followed the procedure, techniques and primers that have been used previously, PCR-RFLP (PCR-restriction fragment length polymorphism) for four genetic variants C597A, L108P, R121W and A105T, and PCR-SSP (PCR-single specific primer) for two other variants V60E and C110G.^{7 19–21} DNA sequencing was performed on 36 samples to verify the results of PCR-RFLP and to detect V60E and C110G mutations where the PCR-SSP failed.

We did not use PCR-RFLP for the two additional variants due to the method and primers used in the findings of V60E and C110G polymorphisms in previous studies²² (Torrente et al²¹) using PCR-SSP.^{21 22} This method allows gene amplification where only a partial sequence information is available even when the information is only known at one end of the DNA fragment. We screened for six variants all within the same exon because some supporting literature states that the majority of mutations are seen in the ‘translated region’ in the third exon of the ND gene.^{23–26} Although in subsequent studies other gene locations were shown that might be associated with ROP, we chose the above-mentioned six genes because they were evaluated in most of the studies. In table 1 we describe the studies on the relationship between ND gene mutations and ROP.

DNA was isolated from the patient’s whole blood, buffy coat or buccal swab. DNA isolation was done using Isolation Kit Gene aid protocols. The DNA obtained from the PCR (DNA fragment sized 297 base pair [bp]) was cut with restriction enzymes to determine the alterations in exon 3. HaeIII restriction enzyme was used to detect C597A polymorphism and L108P mutation, MspI restriction enzyme for R121W mutation, and MboII restriction enzyme for A105T mutation. Subsequently, PCR-RFLP results were visualised by electrophoresis. Optimisation of PCR-SSP wild-type and mutant primer to detect V60E and C110G mutation was carried out using annealing temperatures of 50°C–72°C, primer concentrations of 25 pmol, 30 pmol, 35 pmol and 40 pmol, as well as the addition of dimethyl sulfoxide. Optimisation for the wildtype V60E primer was successfully performed (258

bp). The PCR-SSP for wild-type V60E was performed using an annealing temperature of 57°C and a primer concentration of 30 pmol or 40 pmol. However, optimization of mutant V60E primer, wild-type and mutant C110G primer failed to get the optimal PCR condition. Results for the optimization showed many unspecific bands. Wild-type and mutant C110G primer also produced thick dimers. Therefore, we decided to perform DNA sequencing to verify the results of PCR-RFLP and PCR-SSP.

Results

A total of 182 infants were enrolled in this study. The DNA amplification was performed successfully in 162 samples. The clinical characteristics of the infants are presented in table 2.

Number	Researcher, population	Genetic polymorphism	Screened gene location	Number	Researcher, population	Genetic polymorphism	Screened gene location
1	Shastri <i>et al.</i> , ⁶ USA	R121W and L108P missense mutations.	<i>Exon 3</i>	6	Haider <i>et al.</i> , ²² Kuwait	A105T dan Val160Glu mutations.	<i>Exon 3</i>
2	Buffen <i>et al.</i> , ³¹ (1999), USA	Mutations at 3' UTR.	<i>Exon 1</i>	7	Haider <i>et al.</i> , ¹⁹ Kuwait	AA genotype of C597A polymorphism.	<i>Exon 3</i>
3	Haider <i>et al.</i> , ⁷ Kuwait	R121W and L108P missense mutations.	<i>Exon 3</i>	8	Kim <i>et al.</i> , ⁹ Korea	No gene mutation.	3 exon and their <i>flanking areas</i>
4	Talks <i>et al.</i> , ²⁷ London, UK	Deletions (one 5 bp and the other 71 bp) of the CT repeat sequence in exon 1 of NDP).	<i>Exon 1</i>	9	Hutcheson <i>et al.</i> , ²⁸ various ethnic groups in the USA	Six alterations: 1 in the 5' UTR of exon 2, and 4 in the 3' UTR of <i>exon 3</i> , and the other 14 bp deletion in the 5' UTR of exon 1.	Exons 1, 2, 3, 5' UTR exon 2 and 3' UTR <i>exon 3</i>
5	Hiraoka <i>et al.</i> , ¹¹ USA	Insertion of an additional 12 bp CT repeat and 14 bp deletion in exon 1.	3 exons, splice sites and the 3' UTR region	10	Hiraoka <i>et al.</i> , ¹² Japan	A heterozygous mutation at 5' UTR of exon 1 in the ND gene and a leucine insertion in the signal peptide of LRP5.	3 exon and their <i>flanking areas</i>

Table 2 Clinical characteristic of infants		
Clinical characteristics	ROP positive (cases)	ROP negative (control)
Total (n)	83	79
Birth weight (g)	1182 (529–2430)	1331 (600–2100)
Gestational age (weeks)	30.5 (25–38)	31 (24–35)
Male (%)	38 (45.8)	32 (40.5)
Multiple birth (%)	14 (16.9)	18 (22.8)
Outborn babies (%)	24 (28.9)	23 (29.1)
Low socioeconomic status (%)	30 (36.1)	40 (50.6)
Respiratory disorders (%)	68 (81.9)	76 (96.2)
ICH/IVH (%)	18 (21.7)	11 (13.9)
BPD (%)	14 (16.9)	10 (12.7)
NEC (%)	13 (15.7)	10 (12.7)

BPD, bronchopulmonary dysplasia; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

Birth weight and low socioeconomic status were slightly higher ($p < 0.05$) in the control group, while other characteristics were not different between the groups ($p > 0.05$). Of the infants with ROP, 24 had a birth weight of less than 1000 g and 15 a gestational age of less than 28 weeks. Forty-seven infants with ROP had a birth weight of 1000–1500 g and 43 infants a gestational age of 28–32 weeks. Twelve infants had a birth weight of more than 1500 g. and 25 infants had a gestational age of above 32 weeks (table 3). Fifty-seven infants showed type 2 ROP, while 26 showed type 1 (table 3).

The PCR-RFLP process showed that all samples have wild-type ND genes (table 4). Mutations or polymorphism of C597A, L108P, R121W and A105T were not found in any of the samples collected both from infants with ROP and the control group.

Table 3 Distribution of ROP severity based on birth weight and gestational age

Variable		Cases (n=83)		Control (n=79)
		Type 1 ROP (n=26)	Type 2 ROP (57)	
Birth weight (g)	<1000 (%)	13 (50)	11 (19)	11 (14)
	1000–1500 (%)	13 (50)	34 (59)	46 (58)
	>1500 (%)	0 (0)	12 (21)	22 (28)
Gestational age (weeks)	<28 (%)	12 (46)	3 (5)	8 (10)
	28–32 (%)	9 (35)	34 (60)	44 (56)
	>32 (%)	5 (19)	20 (35)	27 (34)

ROP, retinopathy of prematurity.

DNA sequencing was performed on 36 samples to verify the results of PCR-RFLP and to detect V60E and C110G mutations where the PCR-SSP failed. Samples from 26 infants with ROP and 10 infants from the control group (without ROP) were processed in DNA sequencing. Observed sequences were compared with sequences in GenBank using the BLAST program. The results of BLAST showed 99% homology with Homo sapiens' ND, RefSeqGene on chromosome X with an access code NG 009832.1. Furthermore, the sequences were aligned with GenBank's sequences using ClustalW multiple alignment program. We found no differences in the arrangement of bases compared with the BLAST of the ND gene in six mutation sites, that is, C597A, L108P, R121W, A105T, V60E and C110G, in either cases or controls, in exon 3 (table 5).

Discussion

We did not find any mutations in the ND gene in the 83 infants with ROP as well as in the 79 infants in the control group. This result does not support the hypothesis that this gene may be involved in the development or progression of ROP in infants from Indonesia. Our result cannot explain why

severe ROP is more frequent in Indonesian infants than in infants from other racial backgrounds.

Table 4 Results of the PCR-RFLP and PCR-SSP analyses

ND gene polymorphism/ mutation	Restriction enzymes	Size of PCR product/ND gene	Size after cutting	PCR-RFLP results (n=162)			
				Genotype	Type 1 ROP (n=26)	Type 2 ROP (n=57)	Control (n=79)
C597A	HaeIII	297 bp	CC: 12, 68, 104, 113 bp	CC	26	57	79
			CA: 12, 68, 104, 113, 172 bp	CA	0	0	0
			AA: 12, 113, 172 bp	AA	0	0	0
L108P	HaeIII		LL: 12, 68, 104, 113 bp	LL	26	57	79
			LP: 12, 30, 63, 83, 104, 113 bp	LP	0	0	0
			PP: 12, 30, 68, 83, 104 bp	PP	0	0	0
R121W	MspI		RR: 58, 72, 169 bp	RR	26	57	79
			RW: 58, 72, 130, 169 bp	RW	0	0	0
			WW: 130, 169 bp	WW	0	0	0
A105T	MbolI		AA: 297 bp	AA	26	57	79
			AT: 103, 194, 297 bp	AT	0	0	0
			TT: 103, 194 bp	LL	0	0	0

V60E Not all optimisations for primers on PCR-SSP can be performed.

C110G

ND, Norrie disease; PCR-RFLP, PCR-restriction fragment length polymorphism; PCR-SSP, PCR-single specific primer; ROP, retinopathy of prematurity; bp, base pair.

Table 5 Multiple alignment results of ND gene sequences from samples and ND gene sequences from GenBank

ND gene polymorphism/ mutation	Genotype	DNA sequencing (n=36)		
		Type 1 ROP (n=17)	Type 2 ROP (n=9)	Control (n=10)
C597A	CC	17	9	10
	CA	0	0	0
	AA	0	0	0
L108P	LL	17	9	10
	LP	0	0	0
	PP	0	0	0
R121W	RR	17	9	10
	RW	0	0	0
	WW	0	0	0
A105T	AA	17	9	10
	AT	0	0	0
	TT	0	0	0
V60E	VV	17	9	10
	VG	0	0	0
	GG	0	0	0
C110G	CC	17	9	10
	CG	0	0	0
	GG	0	0	0

ND, Norrie disease; ROP, retinopathy of prematurity.

There are two explanations for our findings. First, there might be variations in the presence of mutations among different countries in Asia. Our results are in line with a study from Korea which also found no mutations in the Norrie gene in infants with ROP.⁹ A study from Hiraoka et al¹² found one infant with a heterozygous mutation in the 5' untranslated region (UTR) of exon 1 ND gene in 17 Japanese infants with advanced ROP and an insertion in the signal peptide of LRP5 in another infant.¹² In another study Hiraoka et al¹¹ failed to find mutations in exons 2 and 3 and the 3' UTR of the ND gene. They found in 100 patients with severe ROP two different mutations in exon 1.¹¹ We did not study these mutations because these mutations were reported only once. Further studies are needed to confirm this possibility.

Second, previous studies have shown inconsistent results regarding the mutations in the ND gene and the development or progression of ROP.^{6-8 10 11 19 27 28} Shastry et al⁶ described missense mutations (R121W and L108P) in 4 out of 16 infants with stage 4 or 5 ROP. In a follow-up study, they found one patient with an insertion in exon 1 and one with a deletion in the same

exon in 100 infants with ROP.¹¹ Haider et al⁷ initially failed to find a relation between mutations in R121W and L108P in infants from Kuwait. Later, he found a polymorphism in the ND gene C597A in 23 out of 24 infants with advanced stage ROP.¹⁹ Talks et al.²⁷ found two patients with a deletion in exon 1 of the ND gene in a group of 22 patients with stage 4 or 5 ROP. On the other hand, Dickinson et al.¹⁰ found no increased incidence of ND mutations in infants with ROP. Hutcheson et al²⁸ found five novel nucleotide changes in 143 infants with severe ROP, one in the 5' UTR region of exon 2 and four in the 3' UTR region of exon 3. They concluded that ND gene polymorphism might play a role in the pathogenesis of ROP, but does not appear to be a major causative factor. Recently, Dailey et al.⁸ found an FZD4 gene mutation, instead of mutations of the ND gene, to be associated with severe ROP. Hartnett²⁹ recently noted a lack of consensus in reports of genetic variants associated with ROP, including VEGF, EPAS1, SOD and the WNT signaling pathway as well as the ND gene. Hartnett et al.³⁰ reported a large study of two cohorts (817 and 543 infants) of US preterm infants with birth weight <1000 g and found a single nucleotide polymorphism (SNP) in the BDNF gene that encodes for brain-derived neurotrophic factor to be significantly associated with severe (threshold) ROP. No mutations in the ND gene were found. We also did not find any mutations in the ND gene in the infants with ROP.

Finally, DNA sequencing was performed on 36 infants. The samples were selected based on a simple random sampling method. The purpose of the sequencing was to detect polymorphisms in all mutations, including V60E and C110G. The χ^2 goodness of fit was used to identify the consistency between the characteristics of the 36 infants and those of the whole group. All variables showed a p value of >0.05, indicating that there were no significant differences between these 36 infants and the whole group. It can be concluded that the 36 samples are representative of the whole group.

A limitation of our study is that we limited the search for mutations in the ND gene to mutations that were described more than once in the literature. We realize that we may have missed mutations, mutations that might be

found especially in infants in Asia. More studies will be needed to screen for more mutations than we did.

Based on our results and previously published studies, we conclude that it is very unlikely that the six polymorphisms in exon 3 of the ND gene studied in this paper are involved in the development or progression of ROP. Further studies must be conducted to find definitive explanations as to why ROP regresses in some patients, while it progresses in others.

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CHAPTER 6

Multicentre Survey of Retinopathy of Prematurity in Indonesia

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Abstract

Background The incidence of retinopathy of prematurity (ROP) is higher in Indonesia than in high-income countries. In order to reduce the incidence of the disease, a protocol on preventing, screening, and treating ROP was published in Indonesia in 2010. To assist the practical implementation of the protocol, meetings were held in all Indonesia regions, calling attention to the high incidence of ROP and the methods to reduce it. In addition, national health insurance was introduced in 2014, making ROP screening and treatment accessible to more infants.

Objective To evaluate whether the introduction of both the guideline drawing attention to the high incidence of ROP and national health insurance may have influenced the incidence of the disease in Indonesia.

Setting Data were collected from 34 hospitals with different levels of care: national referral centers, university-based hospitals, and public and private hospitals.

Methods: A survey was administered with questions on admission numbers, mortality rates, ROP incidence, and its stages for 2016-2017 in relation to gestational age and birth weight.

Results We identified 12,115 eligible infants with a gestational age of less than 34 weeks. Mortality was 24% and any-stage ROP 6.7%. The mortality in infants aged less than 28 weeks was 67%, the incidence of all-stage ROP 18%, and severe ROP 4%. In the 28-32 weeks, the mortality was 24%, all-stage ROP 7%, and severe ROP 4-5%. Both mortality and the incidence of ROP were highest in university-based hospitals.

Conclusions In the 2016-2017 period, the infant mortality rate before 32 weeks of age was higher in Indonesia than in high-income countries, but the incidence of ROP was comparable. This incidence is likely an underestimation due to the high mortality rate. The ROP incidence in 2016-2017 is lower than in surveys conducted before 2015. This decline is likely due to a higher practitioner awareness

about ROP and national health insurance implementation in Indonesia.

Introduction

Studies on the incidence of retinopathy of prematurity (ROP) during the period 2005-2015 in Indonesia showed a relatively high incidence of ROP.^{1,2} ROP was also seen in infants with gestational ages above 32 weeks. In view of these findings, a group of neonatologists and ophthalmologists met in 2009 and 2010 to develop a guideline for the prevention, early detection and management of ROP for neonatologists and ophthalmologists in Indonesia. The national guideline, which was published in 2010, provides advice on how to prevent ROP and how and when to screen newborn infants.³ It recommends screening all infants born before 34 weeks or with a birthweight of less than 1500 g, as well as infants of higher gestational age and higher birth weight who received oxygen for a prolonged period. Neonatologists and paediatric ophthalmologists realized that the guideline's publication had almost no impact on clinical practice. This was most likely due to a lack of knowledge about ROP among paediatricians and ophthalmologists and due to financial constraints in hospitals.

After 2010, the paediatric and ophthalmologist societies in Indonesia therefore organized several meetings to alert their members to the high incidence of ROP and to ways to prevent the disease and perform screening procedures. In addition, national health insurance was introduced in 2014, thereby increasing opportunities to treat premature infants and to improve ROP screening. Care for preterm infants in Indonesia is provided by two national referral centres, university-based NICUs (neonatal intensive care centres), as well as governmental and private hospitals. There are marked variations among these hospitals, such as patients' socioeconomic and cultural backgrounds and other demographic factors, in terms of their options for caring for sick preterm infants. We do not know whether the differences between hospitals resulted in a different incidence of ROP.

To evaluate whether an awareness of the high incidence of ROP and the introduction of national health insurance may have reduced that incidence, we conducted a survey on the incidence of the disease at Indonesian neonatal intensive care centres and local hospitals in the years 2016-2017. As the incidence may differ between hospitals, we collected data from all levels of hospitals that provide care for sick newborns.

Methods

This is a survey: we collected data for the years 2016-2017 in the period from March to November 2019. Paediatricians in 47 hospitals were contacted by email and direct phone calls; 41 were willing to send us the required information. We received responses from 34 hospitals in 17 major provinces of Indonesia – 16 teaching hospitals, two of which are national referral hospitals for perinatology, and 10 government and eight private hospitals. The availability of NICU beds varied greatly across between regions because of a lack of trained neonatologists and differences in stakeholder support in the province or district where the paediatricians worked. We approached hospitals offering all levels of neonatal care, located in all the different parts of Indonesia.

The survey asked for the following data: number of inborn preterm infants, number of preterm infants who died in the perinatal period, number of infants screened for ROP, number of infants with ROP and the stage of ROP. For the sake of uniformity and to analyse all the data, we asked for inborn babies to be further categorised by gestational age and birth weight. For ROP, we used the terms mild ROP (stages 1-2) and severe ROP (stage 3 or higher). We included only inborn infants because important data such as gestational age and complications in pregnancy are often not available for outborn infants. We analysed the university-based hospitals and the district (government)/private hospitals in two separate groups. The data for the two national referral perinatal centres are shown separately. The results are

described in frequencies and percentages. No advance statistical test was used for the data analysis.

Patient involvement

Neither patients nor the public were involved in the design, execution, reporting or dissemination plans for our research.

Results

We received data from the two national referral hospitals for perinatology (Harapan Kita Women and Children's Health Centre and RSCM-Ciptomangunkusumo Hospital), 14 university-based hospital NICUs and 18 other hospitals, which included 10 government hospitals and eight private hospitals (Table 1).

Table 1. Hospital-based ROP data surveillance in Indonesia 2016-2017 (GA $\leq$ 34 weeks)

Type of hospital	Total hospitals	Total infants	Survived	Died		Screened		ROP	
				n	%	n	%	n	%
RSCM/NRH	1	1038	890	148	14.3	392	44.0	7	1.8
HKWCHC	1	478	392	86	18.0	281	71.7	7	2.5
UBH	14	6549	4738	1811	27.7	2041	43.1	197	9.7
OH	18	4050	3261	789	19.5	711	21.8	17	2.4
• Government hospital	10	3020	2425	595	19.7	605	24.9	15	2.5
• Private hospital	8	1030	836	194	18.8	106	12.7	2	1.9
All hospitals	34	12115	9281	2834	23.4	3425	36.9	228	6.7

Note: RSCM/NRH, Ciptomangunkusumo Hospital (national referral hospital); HKWCH, Harapan Kita Women and Children's Hospital (National Centre for Women and Children's Health); UBH, university-based hospital; OH: other hospital; All, all hospitals; ROP, retinopathy of prematurity.

In total, we received data on 12,115 infants with a gestational age <34 weeks, 5,252 of whom had a birth weight of less than 1500 g. The overall mortality of infants <34 weeks was 24.1%. Almost 37% of surviving infants were screened for ROP; the incidence of all-stage ROP was 6.7%. The highest incidence of both mortality and ROP was found in the university-based hospitals (Table 1).

Table 2 shows the data for each hospital or group of hospitals according to gestational age. The overall mortality in the group <28 weeks was 67%, with no differences between hospitals. Sixty-three per cent of surviving infants were screened for ROP. The rate of screening ranged from 93% in one referral hospital to 42% in the 'other hospitals' group. The incidence of both any stage ROP and severe ROP was higher in the university-based NICUs and other hospitals than in the two national centers (18% and 21% vs 4% and 8%) (Figure 1). Severe ROP was not seen in the national centres, but was found in 4% and 5% of infants in the university and other hospitals, respectively. The same trend was found in infants born after 28-32 weeks. Overall mortality in this group was 24%, with the highest mortality in the university hospitals (31%), compared with 11% in one of the national centres. The rate of screening in the group aged 28-32 weeks was lower than in the group aged <28 weeks (41% vs 63%) and ranged from 86% in one national centre to 19% in the 'other hospital' group. Any stage ROP was found in 7% of surviving infants, with the highest incidence (11%) in university hospitals and 1%-2% in other hospitals. The incidence of severe ROP was 0%-1% in all hospitals. The mortality in the group aged 32-34 weeks was 14% on average, with no important differences between hospitals. The rate of screening in these infants was 32% and the prevalence of any stage ROP was 4%, with the highest incidence in university-based hospitals.

Table 2 (A). ROP incidence in Harapan Kita Women and Children's Hospital, Indonesia based on the gestational age in 2005-2017

Variable		Infants GA <28 wks		Infants GA 28 - 32 wks		Infants GA >32 - 34 wks	
		2005-2015	2016-2017	2005-2015	2016-2017	2005-2015	2016-2017
Total (inborn infants)	n	185	54	569	221	NA	203
Died	n	91	27	126	24	-	24
	%	49	50	22	11	-	12
Survived	n	94	27	443	197	-	179
Screened	n	47	25	261	169	156	87
Screened/Survived	%	50	93	59	86	-	49
No ROP	n	28	23	187	167	126	84
ROP 1-2	n	9	2	66	1	29	3
ROP 3-5	n	10	0	8	1	1	0
Prevalence of Any ROP	%	40	8	28	1	19	3
Prevalence of Severe ROP	%	21	0	3	1	1	0

Note: ROP, Retinopathy of Prematurity; GA, gestational age; wks, weeks.

Table 2b. ROP incidence in Indonesia based on the gestational age in 2016-2017

Variable		Infants GA <28 weeks					Infants GA 28 - 32 weeks					Infants GA <32 - 34 weeks				
		2016-2017					2016-2017					2016-2017				
		RSCM	HKWCH	UBH	OH	All	RSCM	HKWCH	UBH	OH	All	RSCM	HKWCH	UBH	OH	All
Total (inborn infants)	n	115	54	903	354	1426	501	221	2288	2044	5054	422	203	3358	1652	5635
Died	n	87	27	577	259	961	122	24	700	349	1195	26	24	534	181	765
	%	76	50	64	73	67	24	11	31	17	24	6	12	16	11	14
Survived	n	28	27	326	95	465	379	197	1588	1695	3859	396	179	2824	1471	4870
Screened	n	23	25	204	40	292	187	169	923	315	1594	182	87	914	356	1539
Screened/Survived	%	82	93	63	42	63	49	86	58	19	41	46	49	32	24	32
No ROP	n	22	23	161	33	239	185	167	751	309	1478	178	84	441	352	1480
ROP 1-2	n	1	2	34	5	42	2	1	94	6	103	2	3	45	2	52
ROP 3-5	n	0	0	9	2	11	0	1	12	0	13	2	0	3	2	7
Prevalence of Any ROP	%	4	8	21	18	18	1	1	11	2	7	2	3	5	1	3.8
Prevalence of Severe ROP	%	0	0	4	5	4	0	1	1	0	1	1	0	0	1	0.4

Note: RSCM/NRH, Ciptomangunkusumo Hospital (national referral hospital); HKWCH, Harapan Kita Women and Children Hospital (National Centre for Women and Children's Health); UBH, university-based hospital; OH, other hospital; All: all hospitals; ROP; Retinopathy of Prematurity; GA, gestational age.

Figure 1: The incidence of ROP based on gestational age in each group of hospitals in Indonesia 2016-2017. HKWCH, Harapan Kita Women and Children's Hospital (National Centre for Women and Children's Health); NRH, National Referral Hospital; OH, other hospitals; ROP, Retinopathy of Prematurity; UBH, University-Based Hospital; wks, weeks.

The online supplemental table shows the data for each hospital or group of hospitals according to birth weight. The overall mortality in the <1000g group was 61%, with no differences between groups of hospitals. Forty-six per cent of surviving infants were screened for ROP; the rate of screening ranged from 88% in one referral hospital to 33% in the 'other hospitals' group. The overall rate of any stage ROP was 18% and severe ROP 3%. The incidence of both any stage ROP and severe ROP was higher in the university-based NICUs and other hospitals than in the two national centres (20% vs 8% and 10%). Severe ROP was not encountered in the national centres but was seen in 3% and 6%, respectively of infants in the university and other hospitals. The same trend was found in infants born with a birth weight of 1000–1500g. Overall mortality in this group was 30%, with the highest mortality in the university and other hospitals (30%), compared with 15% in one of the national centres. The rate of screening in the 1000–1500g group was higher than in the <1000g

group (55% vs 46%), and ranged from 90% in one national centre to 36% in the 'other hospitals' group. Any-stage ROP was found in 8% of surviving infants, with the highest incidence (13%) in the university hospitals and 3% in other hospitals. The incidence of severe ROP was 1% in all hospitals. The mortality in the >1500–2000g group was 12% on average, with no significant differences between hospitals. The rate of screening in these infants was 33% and the prevalence of any stage ROP was 3%, with the highest incidence in university-based hospitals (5%).

Supplementary Table. Incidence of ROP in Indonesia based on the birth weight in 2005-2017

Variable		Inborn infants BW <1000 gram						Inborn infants BW 1000-1500 gram						Inborn infants BW >1500-2000 gram					
		2005-2015	2016-2017					2005-2015	2016-2017					2005-2015	2016-2017				
		HKWCH	RSCM	HKWCH	UBH	OH	All	HKWCH	RSCM	HKWCH	UBH	OH	All	HKWCH	RSCM	HKWCH	UBH	OH	All
Total (Inborn)	n	182	132	71	1024	361	1588	437	306	160	2104	1094	3664	748	475	236	3730	2055	6496
Died	n	85	101	38	567	256	962	72	93	24	640	346	1103	.	42	24	532	205	803
	%	47	77	54	55	71	61	16	30	15	30	32	30	.	9	10	14	10	12
Survived	n	97	31	33	457	105	626	365	213	136	1464	748	2561	.	433	212	3198	1850	5693
Screened	n	59	26	29	197	35	287	252	169	123	802	273	1413	163	177	54	1131	495	1857
Screened/ Survived	%	61	84	88	43	33	46	69	79	90	55	36	55	.	41	25	35	27	33
No ROP	n	27	24	26	156	28	234	172	167	120	696	265	1248	139	175	53	488	492	1208
ROP 1-2	n	22	2	2	33	5	42	71	1	3	89	7	100	22	1	1	54	2	58
ROP 3-5	n	10	0	1	6	2	9	9	1	0	17	1	19	2	1	0	0	1	2
Prevalence of Any ROP	%	54	8	10	20	20	18	32	1	2	13	3	8	15	1	2	5	1	3
Prevalence of Severe ROP	%	17	0	3	3	6	3	4	1	0	2	0	1	1	1	0	0	0	0

Note: RSCM/NRH: Ciptomangunkusumo Hospital (National Referral Hospital); HKWCH: Harapan Kita Women and Children Hospital (National Centre for Women and Children's Health); UBH: University Based Hospital; OH: Other Hospital; All: All Hospital; ROP; Retinopathy of Prematurity; BW: Birth weight.

In order to assess whether the screening rate may have affected the incidence of ROP found in our survey, we calculated the incidence of ROP in 13 of the 34 hospitals where at least 80% of infants were screened once or more (table 3). There was no difference in the rate of ROP between these hospitals and the total group. In the <28 weeks group, the ROP rate at all stages was 21% and 5% for severe ROP. In the 28-32 weeks group, the incidence of all ROP stages was 6% and severe ROP 1%.

Table 3. Incidence of ROP in hospitals with 80% screening coverage in Indonesia, 2016-2017

Variable		Birth weight					Gestational age				
		<1000 g	1000-1500 g	>1500-2000 g	>2000-2500 g	≥2500 g	<28 wks	28-32 wks	32-34 wks	34-37 wks	≥37 wks
Total (inborn)	n	585	1541	2679	4522	20572	560	2144	2319	3913	20963
Died	n	394	449	303	163	266	391	508	244	165	267
	%	67	29	11	4	1	70	24	11	4	1
Survived	n	191	1092	2376	4359	20306	169	1636	2075	3748	20696
Screened	n	172	1040	1033	1186	14	168	1147	926	1199	5
Screened/ Survived	%	90	95	43	27	0	99	70	45	32	0
No ROP	n	137	966	978	1159	14	132	1074	874	1169	5
ROP 1-2	n	28	57	53	27	0	27	62	46	30	0
ROP 3-5	n	7	17	2	0	0	9	11	6	0	0
Incidence of Any ROP	%	20	7	5	2	0	21	6	6	3	0
Incidence of Severe ROP	%	4	2	0	0	0	5	1	1	0	0

Note: these data come from 13 of 34 hospitals; ROP, retinopathy of prematurity

Discussion

Globally, ROP is one of the hidden causes of morbidity following death-related problems such as respiratory distress (asphyxia), infections and other complications that arise in small, sick preterm infants. Countries with a high rate of premature births will consequently see a higher number of infants affected by ROP. This situation occurs in almost all parts of the world, both in high-income (HIC) and lower/middle income countries (LMIC).⁴

What has been characterised as the third ROP epidemic has particularly affected countries in Southeast Asia. It is clear that many cases of visual impairment due to ROP are preventable through improved neonatal care, timely retinal examination and appropriate treatment.⁵ In this survey, we present data on the incidence and severity of ROP following the implementation of a national guideline for the prevention, screening and treatment of ROP and the introduction of national health insurance in Indonesia, one of the major regions in Southeast Asia.

This survey conducted in 2016-2017 found the incidence of ROP in Indonesia in that period to be much lower than the incidence we found in 2005-2015.^{1,2} In that previous period, we found in one NICU a 40% incidence of all-stage ROP in infants below 28 weeks and a 28% incidence in the 28-32 week group.¹ Other studies from the period 2005-2015 in Indonesia found a ROP incidence of 18-30% in infants born before 32 weeks and/or with a birth weight of less than 1500 g.² Different factors may have contributed to this marked decline in ROP. First, a national guideline for ROP prevention and screening was published in 2010. When we realized that simply publishing this guideline did not change practices in Indonesia, several focus meetings were held across the country to alert practitioners to the high incidence of ROP, the methods to prevent ROP and the importance of screening.³ In addition, national health insurance was introduced in 2014, thereby improving opportunities for treating and screening preterm infants. We cannot identify which of these factors may have had the greatest impact on the decline in incidence of ROP.

It is difficult to compare the incidence of ROP in Indonesia with the incidence reported in HIC. A recent study from Greece showed an incidence of any stage ROP in infants <32 weeks of 19.7% and severe ROP 7.4%.⁶ The EXPRESS study from Sweden found an incidence of any stage ROP in infants <31 weeks of 31.9% and severe ROP 5.7%.⁷ There is a marked difference, however, between Indonesia and HIC in the type of infants cared for and their survival. In Indonesia, almost no infants born after a gestational age of 26 weeks or less will survive. Mortality among infants of 26-28 weeks is much higher than in HIC. In our survey, we found that 67% of infants born <28 weeks died. Recent data from Sweden, England, France, the Netherlands, Canada and the USA show a survival rate for infants born between 26 and 28 weeks of 80-90%.⁸⁻¹⁸ In Indonesia, only the healthier very preterm infants will survive. The incidence of ROP may be lower in these infants than in the very sick newborns who died. The same may be true of infants born after 28-32 weeks. In Indonesia, we found that 24% of these infants died. In HIC, that figure is less than 5%. The present data on the incidence of ROP in Indonesia could be an underestimation caused by the higher death rate in Indonesia. There are more reasons why our data might be an underestimation of the real incidence of ROP in Indonesia. Not all hospitals in Indonesia have an ophthalmologist, and therefore not all preterm infants are screened. Screening might not be according to the recommended schedule in all infants so that ROP can be missed even in screened infants. Infants might be too sick to be screened, and infants might not be screened after discharge.

Studies conducted in other LMIC up to 2015 also showed a higher incidence of ROP than in HIC. In addition, ROP was seen in infants with a higher gestational age and birth weight. A study from the Philippines showed a ROP incidence of 14% in all infants born before 36 weeks.¹⁹ A small study from Brunei showed a prevalence of 35% in infants with a birth weight of 1300±500 g and a gestational age of 29.5±2.6 weeks.²⁰ In Thailand, a ROP incidence of 14% was found in infants with a mean birthweight of 1514 g and a gestational age of 31.8 weeks.²¹ In India, ROP has been reported to occur in 21.7%– 51.9% of low birthweight infants. Most studies reported the mean birth weight of babies developing ROP to be above 1250 g and the incidence of severe

ROP ranging from 5.0–44.9%.²² In line with our findings for the period 2005-2015, these data indicate that ROP is prevalent in LMIC, including in infants with a higher birthweight and gestational age. A recent paper describes the current state of ROP in eight LMIC.²³ The incidence of ROP was not available for all countries. This incidence, mostly based on smaller studies in one institution, ranged from 14% to 50%. In almost all countries, infants up to 34 weeks and with a birth weight of 2000 g were screened. A study from Thailand, where only infants born <30 weeks and with a birth weight of <1500 g were screened, found a ROP incidence of 40%. In all countries, the screening rate was low, at <35%. The reasons mentioned for the high incidence of ROP was similar for all countries: a lack of awareness among paediatricians, a shortage of trained ophthalmologists and a lack of funds for screening. Almost all countries lacked oxygen delivery systems and oxygen saturation monitors. All countries fear an epidemic of blind infants as a result of ROP. In our view, the results of our survey indicate that it is possible to reduce the incidence of ROP, also in LMIC. The first step to stop this epidemic is to be aware of the risks of ROP. This concerns all those involved in the care of preterm infants, paediatricians, ophthalmologists, nurses and administrators.

Our study found that the screening rate for ROP is rather low in Indonesia, both in infants with a low gestational age and in infants with a higher gestational age who received supplemental oxygen for a prolonged period. This is most likely due to at least three factors: a lack of trained ophthalmologists, a lack of awareness among paediatricians of the importance of screening and a lack of funding for ophthalmologists. Paediatric ophthalmologists are mainly found in large academic hospitals and the national centres for perinatology. In almost all cases, there is only one paediatric ophthalmologist who is not always available. In order to increase the screening rate, paediatricians must be made aware of its importance and ophthalmologists must be trained to do it. Funds to carry out the screening need to be made available. It will not be possible to have, in a short period, enough trained ophthalmologists in Indonesia to have all preterm infants requiring ROP screening, screened according to the international accepted screening protocols. A potential solution to the

lack of trained ophthalmologists might be cameras to make images of the retina and have these images evaluated by qualified, non-medical personnel. These assistants can send pictures of infants who might need ROP treatment via the internet to trained ophthalmologists. Simple, not expensive cameras have been developed. This system's advantage is that time required be made in smaller hospitals without a trained ophthalmologists. This system is now implemented in India's parts, where it has been shown to be very effective. A sensitivity of 98% is achieved in detecting ROP cases that need intervention.^{24,25}

We found no difference in the incidence of ROP in the institutions with a screening rate of at least 80%, compared to the whole group of infants. This indicates that a high number of infants are not screened while they develop ROP. The follow-up of preterm infants admitted to a NICU is low in Indonesia because of socioeconomic factors. It is not therefore known how often ROP was present in surviving, unscreened infants.

A lack of ophthalmologists trained in ROP screening is not a problem that is unique to Indonesia. There is a shortage of trained ophthalmologists in many LMIC and, where they do exist, screening is often not properly reimbursed and only the most committed ophthalmologists are willing to screen.²⁶

In addition, paediatricians participating in this survey reported a reluctance among ophthalmologists to screen because of medico-legal problems, an imbalance between the level of difficulty and time spent examining very small premature babies and the results obtained, and the asynchronous examination fees in different health insurance systems. This all contrasts with the practice in HIC, where failure to screen an eligible infant for ROP could be considered malpractice.

The incidence of ROP in Harapan Kita Women and Children's Hospital was significantly lower in the period 2016-2017 than in the period 2005-2015. At the same time, the screening rate improved to 93%. This indicates that ROP declined significantly at that hospital. In 2016, a strict policy was introduced to set the oxygen saturation monitor at

91% to 95% for preterm infants. The use of oxygen in the delivery room was also strictly regulated, with resuscitation of preterm infants starting at 30% oxygen. Continuous positive airway pressure was given directly after birth and continued in the NICU. These measures are likely to have played an important role in reducing the incidence of ROP at that NICU.

The highest rate of both mortality and ROP was found in the university-based hospitals. These are referral hospitals that admit mothers with antenatal complications. They may therefore treat the sickest infants, sicker than those cared for in governmental and private hospitals. This could explain the higher rate of mortality and ROP. At the same time, however, the two national centres are also referral hospitals and they showed a lower mortality rate and a lower incidence of ROP (figures 1 and 2). This suggests that there could be other factors behind the higher incidence of ROP in the university-based hospitals. More liberal use of oxygen might be a cause. More studies are needed to determine the cause of the less favourable outcome in the university-based hospitals.

Figure 2: Mortality based on the gestational age in each group of hospitals in Indonesia 2016-2017. HKWCH, Harapan Kita Women and Children Hospital (Health Center); NRH, National Referral Hospital; OH, other hospitals; UBH, University-Based Hospital; wks, weeks.

A limitation of this study is that the survey on the incidence of ROP as carried out in this study had not been done before. As a reference in this paper, we used data from one referral hospital as well as data from the literature. The rates of ROP found in one hospital in Indonesia¹ and the studies done in other centres² all showed a high incidence of ROP in the period before 2015. Therefore, we are convinced that the incidence of ROP was indeed much higher than suggested by the results of this survey. A second limitation of our survey is that we only included inborn infants. We do not have precise data on the ratio of inborn and outborn infants for all hospitals. In the Harapan Kita Hospital, one of the national referral hospitals, on average 71% of the admitted infants are inborn. We estimate that this percentage will be almost the same for the university-based NICUs. Unfortunately, there is no adequate neonatal transport service in Indonesia. Transportation is carried out by poorly trained personnel and only 100% oxygen can be given during transport. The referring and accepting neonatologists do not meet, making the transfer of information difficult and often incomplete.

Conclusion

The incidence of ROP in preterm infants in Indonesia was lower in 2016-2017 than in the period before 2015. This may be due to a higher awareness of ROP among practitioners and the introduction of a national health-care plan. Our data, however are likely to be an underestimation of the real incidence of ROP because of the higher mortality rate among small premature infants in Indonesia than in HIC and a low rate of screening and follow-up of surviving preterm infants.

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(including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis.

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What is already known on this topic?

- Several studies in the previous decade in Indonesia showed a high incidence of ROP, which is a serious problem, as in other LMIC countries.

- The high rate of ROP in Indonesia is likely due to the expansion of neonatal intensive care, whereas there is a lack of awareness of the risks of developing ROP.

What does this study add?

- The incidence of ROP in Indonesia was lower in 2016-2017 than in surveys conducted before 2015.
- There was a difference in mortality and rate of ROP between the types of hospital. Both mortality and the incidence of ROP were highest in university-based hospitals.
- The lower rate of ROP could be the result of a new national guideline on ROP, an increased awareness following meetings and the introduction of national health care.

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CHAPTER 7

How to prevent ROP in preterm infants in Indonesia?

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Abstract

Background and Aims: Retinopathy of prematurity (ROP) is a severe disease in preterm infants. It is seen more frequently in Low-Middle Income Countries (LMIC) like Indonesia compared to High-Income Countries (HIC). Risk factors for ROP development are -extreme- preterm birth, use of oxygen, neonatal infections, respiratory problems, inadequate nutrition and blood, and exchange transfusions. In this paper, we give an overview of steps that can be taken in LMIC to prevent ROP and provide guidelines for screening and treating ROP.

Methods: Based on the literature search and data obtained by us in Indonesia's studies, we propose guidelines for the prevention, screening, and treatment of ROP in preterm infants in LMIC.

Results: Prevention of ROP starts before birth with preventing preterm labor, transferring a mother who might deliver <32 weeks to a perinatal center, and giving corticosteroids to mothers that might deliver <34 weeks. Newborn resuscitation must be done using room air or, in case of very preterm infants (<29-32 weeks) by using 30% oxygen. Respiratory problems must be prevented by starting continuous positive airway pressure (CPAP) in all preterm infants <32 weeks and in case of respiratory problems in more mature infants. If needed, the surfactant should be given in a minimally invasive manner, as ROP's lower incidence was found using this technique. The use of oxygen must be strictly regulated with a saturation monitor of 91-95%. Infections must be prevented as much as possible. Both oral and parenteral nutrition must be started in all preterm infants on day one of life with preferably mothers' milk. Blood transfusions can be prevented by reducing the amount of blood needed for laboratory analysis.

Discussion: Preterm babies should be born in facilities able to care for them optimally. The use of oxygen must be strictly regulated. ROP screening is mandatory in infants born <34 weeks, and infants who received

supplemental oxygen for a prolonged period. In case of progression of ROP, immediate mandatory treatment is required.

Conclusion: Concerted action is needed to reduce the incidence of ROP in LMIC. “STOP – R1O2P3” is an acronym that can help implement standard practices in all neonatal intensive care units in LMIC to prevent development and progression.

Keywords: low-middle income countries, predisposing factors, recommendation, ROP, screening

1. Introduction

Retinopathy of prematurity (ROP) is a severe disease that might result in blindness. It is seen in preterm infants with increasing incidence alongside the shorter duration of pregnancy. To a great extent, the disease is preventable via strict control of oxygen delivery to the newborn infant. ROP is seen more frequently in Indonesia as compared to High-Income Countries (HIC). It is also seen in infants with gestational age above 32 weeks, a group of infants where ROP is not seen in HIC. In Indonesia, the reported incidence of all stages of ROP in infants <32 weeks ranged from 18–30%.^[3] We studied the incidence in the NICU of Harapan Kita Women and Children Hospital, Jakarta, as one of NICUs' role models in Indonesia. We found that 40 percent of infants with a GA of <28 weeks had ROP all stages, and 21% showed stage >3 ROP. Also concerning is the incidence of ROP in our patients with a GA of 28–32 weeks where any stage ROP was found in 29%, and stage >3 ROP in 3% of the screened infants.^[4] In comparison, the incidence of any stage ROP in developed countries (NMR <5) is approximately 21.8% in infants with a gestational age of less than 32 weeks^[5] and the incidence of ROP III-V in infants with a gestational age of less than 26 weeks is 10%.^[6] Many studies have shown that there are three main risk factors for the development of ROP. First, the shorter the gestational age, the higher the risk. Second, the

lower the birthweight, the higher the risk. Finally, there is a clear correlation between the oxygen concentration in inspired air in the first weeks of life and the development of ROP.

Preventing ROP already starts before birth by preventing preterm labor and intrauterine growth retardation. After birth, strict control of oxygen delivery is needed, and neonatal disease should be prevented as much as possible. In this article, we give recommendations on reducing the high ROP incidence in a low-middle income countries (LMIC) like Indonesia.

2. Search Major Risk Factors of ROP

2.1. Gestational age at birth and birthweight

2.1.1. Background

Gestational age at birth (GA) and birth weight (BW) are the most substantial known risk factors for the development of ROP. The most effective way to reduce the incidence of ROP is to prevent preterm delivery. A 100-gram increase in BW decreases the odds of severe ROP with 27%, and each week increase in GA decreases the incidence of severe ROP with 19%.^[7] Although preterm birth cannot always be prevented, optimal antenatal care can reduce the incidence. Early recognition and treatment of pregnancy complications, such as hypertension, pre-eclampsia, maternal malnutrition, maternal diabetes, and the mother's infections, will reduce prematurity incidence. The mother's smoking habits are also another risk factor for the development of ROP as smoking will result in intrauterine growth retardation.^[8]

2.1.2. Clinical Management

Pregnant women with complications in pregnancy before 32 weeks must be referred to a center with experienced obstetricians and an NICU where full adequate support can be given to the pregnant mothers and infants of less than 32 weeks.

2.2. Supplemental oxygen

2.2.1. Background

The immature retina of a preterm infant is susceptible to insults that disrupt neuro-vascular growth, leading to ROP. Suppression of growth factors due to hyperoxia results in an arrest of retinal vascularization (phase 1). Subsequently, the increasing metabolically active, yet poorly vascularized retina becomes hypoxic, stimulating growth factor-induced vasoproliferation (phase 2), which eventually can cause retinal detachment.^[9]

Giving supplemental oxygen that results in high oxygen tension and saturation is a significant risk factor for the development of ROP. Studies have convincingly shown that restricting the use of oxygen in the first weeks after birth reduces the incidence of ROP.^[10] Both the concentration of oxygen is given, and the resulting oxygen saturation must be controlled. Oxygen blenders control the percentage of oxygen given, and transcutaneous oxygen saturation monitors are the most widely used systems to control the oxygen saturation in the blood.

2.2.2. Clinical management

Many studies have evaluated the most optimal setting of oxygen saturation limits.^[10] Setting the low limits of the saturation monitor at 84% is related to an increased death rate. Setting the upper limit of the monitor above 95% increases the risk of developing ROP. Based on several studies,^[11,12] it is advisable to aim for a saturation between 91 and 95%. To achieve this, the oxygen saturation monitor's alarm limits should be set between 90 and 96%.^[13]

The supplemental oxygen should be controlled in each newborn by close monitoring the oxygen concentration administered and the resulting oxygen saturation in the infant. Infants should not be treated in a facility where these systems are not available, and they must be transferred to a facility where these systems are available. In all hospitals where infants are born, oxygen blenders must be available, both in the delivery room and in the neonatal ward. In case no oxygen blender is available, oxygen must be

diluted with room air because 100% oxygen is extremely hazardous for the newborn infant. The desired oxygen concentration can be calculated using the following formula $\{(n_1 \times 21) + (n_2 \times 100)\} : (n_1 + n_2)$ (n_1 is the flowrate of air, n_2 the flowrate of oxygen). A 60% oxygen concentration will be obtained from diluting 1 L/min of oxygen with 1 L/min of air. When 2 L/min of room air is given together with 1 L/min of oxygen, the resulting oxygen concentration is 47%. When 3 L/min of room air is given together with 1 L/min of oxygen, the resulting oxygen concentration is 37%. A scheme "rules of eight" how to dilute oxygen and the resulting oxygen concentration is given in Table 1. The oxygen concentration in the oxygen/air mixture can be calculated using the following formula

$$\frac{n.100 + (8-n).21}{8} = \text{percentage oxygen}$$

Oxygen concentration should be titrated according to the values found with the oxygen saturation monitor. In case no oxygen saturation monitor is available, the concentration of supplemental oxygen should be reduced to a level where the first signs of cyanosis are present, whereafter, the oxygen concentration is increased with 5% to 10%.^[14] Fluctuations in the oxygen saturation must be prevented since fluctuations and periods with hyper- and hypoxia have been shown to increase the risk for ROP.^[15] There is no need to use medical gas as compressed air. As used for diving, compressed air can safely be used for the newborn infant when flowmeters are available that can deliver amounts of 1 to 10 L/min.

Table 1. Oxygen concentration resulting from mixing air and oxygen.

Pure Oxygen (100%) L/min	Pressurized air (oxygen 21%) L/min	Resulting oxygen concentration (%)
0	8 (0.5 -10)	21
0.25	7.75 (7,5 – 7.75)	23
0.5	7.5 (7- 10)	26 (25 – 26)
1	7 (7- 9)	31 (29 – 31)
2	6	40
3	5	51
4	4	61
5	3	70
6	2	80
7	1	90
8 (0.5 – 10)	0	100

3. OTHER FACTORS INCREASING THE RISK TO DEVELOP ROP.

3.1. Maternal factors

3.1.1. Background

Hypertension in pregnant mothers is suggested to increase the risk of ROP by influencing vascular growth factors. A meta-analysis found, however, no relation between hypertension in the mother and ROP.^[16] Smoking is a risk factor, most likely to cause growth restriction due to smoking.^[17] Chorioamnionitis might increase the risk of ROP by both preterm birth and inflammatory mediators, as shown in a recent review on risk factors for ROP.^[18] Giving corticosteroids to mothers who might deliver before 32 weeks reduces the risk for BPD. This medication is related to less severe lung problems and more general aging effects of corticosteroids.^[19,20] A lower incidence of BPD will result in less oxygen supplementation to the infant and thereby a lower risk of developing ROP.

3.1.2. Clinical management

Optimal antenatal care is essential to reduce the risk of preterm labor and improve the fetus's condition. Transferring a pregnant mother to a center is mandatory in case of complications in pregnancy below 32 weeks. Mothers with severe complications at higher gestational ages also must be referred. A course of corticosteroids, 12 mg betamethasone for two days, should be given to all mothers who might deliver before 34 weeks.

3.2. Place of delivery

3.2.1. Background

The risk of developing ROP is higher in infants who have severe illness in the post-natal period. The risk of developing severe ROP is higher for an infant born in a hospital not equipped with adequate facilities or a hospital without well-trained personnel. This risk is also higher when a child needs a post-natal transfer to the NICU, as found both in the CRYO-ROP and ET-ROP studies.^[21,22]

3.2.2. Clinical management

An important method to reduce the incidence of ROP, therefore is to transfer a mother (before delivery) to a center with a neonatal intensive care unit where next to controlling oxygen delivery and oxygen saturation, full support for a very preterm infant is possible. All mothers who might deliver before 32 weeks should be transferred to that perinatal center, while those who might deliver between 32 and 36 weeks should be transferred to district hospitals or alternative hospitals with a newborn intensive care center to anticipate for possible intensive care that might be needed by the infant after birth.

3.3. Infant factors

3.3.1. Resuscitation

Background

In almost all cases, it is unnecessary to administer supplemental oxygen when resuscitating term or preterm infants. The outcome of resuscitation is not better when 100% oxygen is given, compared to room air. Resuscitation with 100% oxygen will induce oxygen radicals, which are incredibly toxic for newborn infants. Lower levels of oxygen scavengers, compounds that reduce oxygen toxicity, are seen up to 4 weeks after resuscitation with 100% oxygen. The oxygen radicals might induce the development of ROP later on.^[23] Therefore, international resuscitation counsels advise that they use room air to resuscitate term infants and infants of 32 weeks and higher. There is a slow increase in oxygen saturation in all healthy, term and preterm infants after birth^[13] [Figure 1]. This saturation indicates no need to give supplemental oxygen when the oxygen saturation is still 75 to 80% 5 minutes after birth.

Figure 1 Oxygen saturation in the first 10 minutes after birth (3rd, 10th, 25th, 50th, 75th, 90th, and 97th, SpO₂ percentiles for all preterm and term infants with no medical intervention after birth)¹³

In infants born after 28-32 weeks, it is advised to resuscitate with 21-30% oxygen, after less than 28 weeks with 30% oxygen. A meta-analysis by Saugstad et al. showed that preterm babies ≤ 32 weeks' gestation resuscitated with lower (0.21–0.3) versus higher (0.6–1.0) initial FiO_2 showed no differences in morbidity but exhibited an almost significant trend towards reduced mortality.^[24] A Systematic Review with meta-analysis published in 2019 by Welsford et al. concluded that preterm newborns' ideal initial FiO_2 is still unknown. However, the majority of newborns' ≤ 32 weeks' gestation will require some oxygen supplementation.^[25] Suggestions regarding the amount FiO_2 that should be given to newborn infants in the delivery room and the corresponding SpO_2 targets are shown in table 2.^[23,26]

Table 2. Suggestions regarding the amount of oxygen supplementation in the delivery room.

Gestational Age	Initial FiO_2	Target SpO_2 at 5 min
>37 weeks	0.21	85 – 90%
33 ⁺⁰ to 36 ⁺⁶ weeks	0.21	85
29 ⁺⁰ to 32 ⁺⁶ weeks	0.21 – 0.30	80 – 85%
≤ 28 weeks	0.3	80%

Note: [Lara-Cantón I et al. Children 2019⁽²⁶⁾ - modified from Saugstad et al. Pediatr Res 2019⁽²³⁾]

Practical Clinical management.

Resuscitation in term infants and infants born after at least 32 weeks must be started using room air. At a gestational age of 28 to 32 weeks, the advice is to resuscitate with 21% to 30% oxygen.^[13] Higher levels of oxygen are indicated when the goals for oxygen saturation, as described above, are not reached. These guidelines conform to the recommendations of the National Resuscitation Foundation.^[27,28]

In cases where supplemental oxygen is given, the resulting oxygen saturation must be monitored. The amount of oxygen given must be controlled by using an air/oxygen blender. In cases where the blender is not

available, resuscitation with a mixture of 3.5 L/min room air and 0.5 L/min oxygen, resulting in a mixture with 30% oxygen, is sufficient in almost all cases.

3.3.2. Optimal nutrition and growth.

Background

Infants with a low weight gain after birth have a higher risk of developing ROP as compared to those who gain weight following the intrauterine growth curve.^[7] Low weight gain can be caused by low nutrient intake. However, it can also be an indicator of severe illness. Studies have shown that a deficiency of specific nutrients, particularly n-3 poly-unsaturated essential fatty acids is related to a higher risk of ROP development.^[29] Many TPN solutions contain only small amounts of these fatty acids. In cases of severe illnesses, there might be a low weight gain and corresponding low IGF-1 levels. IGF-1 is an anabolic hormone promoting anabolism of many tissues, including retinal vessels. Low IGF-1 levels are associated with increased risks for ROP.^[30] Hyperglycemia is related to ROP's higher incidences, while hyperglycemia is mainly seen in extremely sick and preterm infants.^[9] Severe illness increases the risk of developing ROP, most likely through the presence of pro-inflammatory cytokines.^[31] Human milk is recommended to all preterm infants after birth and effectively prevents necrotizing enterocolitis and late-onset sepsis.^[32,33] Human milk has also been shown to reduce the incidence of ROP.^[34-36] This might be due to a number of antioxidant components that could be potentially protective against ROP or the presence of long chain polyunsaturated fatty acids in human milk.^[9]

Clinical Management

Starting nutrition on the first day after birth is essential. Enteral feeding can be started in almost all infants on the first day with preferably human milk at a dose of 10 to 20 mL/kg BW/day and increased with 20 mL/kg/day. Starting parenteral feeding with amino acids at a dose of 2 to 3 g/kg BW/day and lipids in a dose of 1 g/kg/day directly after birth are essential to prevent

muscle breakdown, promote muscle breakdown, and optimize the immune response.

3.3.3. Respiratory problems

Background

Respiratory problems and the use of various techniques to treat these problems, such as mechanical ventilation, high-frequency oscillation, and continuous positive airway pressure (CPAP), are associated with a higher incidence of ROP.^[37,38] Treating respiratory problems is related to the incidence of ROP, most likely due to supplemental oxygen. The more oxygen is used, and the longer the duration of respiratory support, the higher risk of developing ROP. Therefore, preventing respiratory problems and shortening respiratory support by lung-protective ventilation strategies are most important in preventing ROP.

Clinical Management

Corticosteroids should be given to mothers threatening to deliver <34 weeks. Start with CPAP in all preterm infant <32 weeks. Give surfactant when oxygen needs >40%, especially when a CPAP level of 8 to 12 cm H₂O is needed to reach sufficient oxygen saturation.^[39,40] Recent studies^[1,2] showed a lower incidence of ROP in infants treated with minimally invasive surfactants administration compared to endotracheal intubation. Use lung-protective ventilation strategies by using only synchronized ventilation modes with volume guarantee, limit tidal volumes to 5-7 mL/kg BW, and use at least 5 cm PEEP. Be aggressive in weaning from the ventilator and extubate as soon as possible.

3.3.4. Prevention of Late Onset Sepsis

Background

Infections, particularly late-onset sepsis (LOS), increase the risk of developing ROP.^[41,42] Pro-inflammatory compounds such as prostaglandins and cytokines influence the development of the vasculature, thereby developing ROP.^[43]

Clinical Management

The risk of newborn infants to develop LOS is highly dependent on the quality of care in the NICU. Proper hygiene policies such as strict handwashing protocols, clean materials, and aseptic procedures decrease the risk. The risk to develop LOS is lower in infants who are gaining weight well, and who have not been treated with broad-spectrum antibiotics.

3.3.5. Blood and Exchange Transfusion

Background

Many studies showed that blood transfusions increase the risk of ROP.^[44-46] A study in Indonesia showed that the risk was also increased when an exchange transfusion was done.^[47] The increased risk might be due to either the administration of adult hemoglobin or the iron overload resulting from the transfusions. Iron overload increases the risks of oxygen radicals. Adult hemoglobin causes a higher delivery of oxygen to tissues compared to fetal hemoglobin. Some studies found that anemia was related to an increased risk of ROP, as well as the administration of EPO.^[48] Delayed umbilical cord clamping – DCC – (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes.^[49] In preterm infants, delayed umbilical cord clamping is associated with significant neonatal benefits, including the better establishment of red blood cell volume and decreased need for blood transfusion.^[50] This intervention is appropriate not only in sick but also in stable preterm who do not require positive pressure ventilation. DCC intervention should be considered because iron deficiency anemia is one of the four significant malnutrition problems in vulnerable age groups, including pregnant mothers in Indonesia, next to protein-energy deficiency, vitamin A deficiency, and iodine deficiency. Preventing anemia by delayed cord clamping, therefore, is of special advantage in Indonesia. Hyperbilirubinemia is an increased serum bilirubin level that can be prevented by early determination of the bilirubin level. Early identification of increased bilirubin levels will reduce the need for exchange transfusions.^[51]

Clinical Management

The most frequent reason for blood transfusion is blood taking. Micro methods for laboratory determinations are needed. Regarding the implementation of DCC for the prevention of anemia in premature infants in Indonesia, we tried to implement this routine in our hospital. Unfortunately, there is no detailed data regarding the use of DCC in our country. National guidelines are needed so that this relatively easy-to-perform procedure can be widely implemented. Hyperbilirubinemia must be prevented by early determination of increased serum bilirubin, together with early use of phototherapy.

4. STOP – R102P3

We created the mnemonic **"STOP - R102P3"** to make it easier to remember the steps to be taken to prevent ROP.

4.1. S (Start)

To stop ROP, it starts with preventing ROP antenatally by preventing preterm birth by referring to the mother. She might deliver before 32 weeks to a perinatal center and give corticosteroids to the mother in case of threatening preterm labor <34 weeks.

4.2. T (Tiered referral system)

Improvement of neonatal care facilities must start in the regional general hospital and continue in the referral hospital. A tiered standard referral system is needed to make it possible for patients to get services that meet their needs. Stakeholders must realize the establishment of regional perinatal/neonatal intensive care centers with complete facilities. Mothers with complications in pregnancy and tiny VLBW infants at high risk must be sent to the hospital with a tiered referral system.

- Complications in pregnancy < 32 weeks – send the mother to the hospital with NICU
- Complications in pregnancy 32 to 36 weeks – send the mother to the hospital with NICU or district hospital
- An infant born <32 weeks or birth weight <1250 g – send to hospital with NICU
- An infant born 32 to 34 weeks or birth weight 1250 to 1500 g – send to a district hospital

4.3. O (Ophthalmology Screening and Treatment)

4.3.1. Screening infants for ROP

Background

Most cases of ROP resolve naturally. However, there will be progression to severe disease in some infants that might lead to blindness. When the progression of ROP to severe stages is detected in time, treatment can prevent blindness progression. Therefore, all infants with a risk to develop ROP must be screened. Screening protocols are published, mainly for HIC countries.^[52-55] They include a screening of all infants born before 32 weeks. The screening usually starts at 4 to 6 weeks postnatally (but at least 31 weeks postmenstrual age) and continues until the retina's complete vascularization. However, these guidelines need adaptation for Indonesia, as ROP is also seen in infants with gestational ages above 32 weeks. We developed the National ROP Screening and Treatment Guideline for preterm babies in Indonesia at National Neonatologist-Ophthalmologist Workshops, which should be used in all NICUs in Indonesia.^[56] These guidelines advise the following indications for ROP screening:^[56,57]

- Screen all infants born before ≤ 34 weeks and/or BW ≤ 1500 g.
- Infants with greater BW or older GA should be screened for ROP in case the infants received supplemental oxygen, either at birth or in the first weeks of life. This screening can be requested by a neonatologist or pediatrician and depends on the severity of neonatal risk factors.

Figure 2. Scheme of the retina of both eyes showing three-zone borders and clock hours used to describe the location and extent of retinopathy of prematurity.⁵⁸

Time of First Examination

If the GA is more than 30 weeks, baby is examined 2 to 4 weeks after birth

- If the GA is less than or equal to 30 weeks, check 4 weeks after birth
- Infants with 37 weeks or more gestational age do not need to do ROP screening
- At least one examination before discharge from the hospital

Further screening depends on the findings of the first examination

- Repeat screening every week or 2 weeks until complete vascularization or ROP is confirmed
- Continue screening until there is complete regression.
- If ROP is progressing to type 1 ROP, urgent treatment is needed.
- It is necessary to monitor the infants after discharge to ensure that their disease does not develop into stages requiring treatment.
- Infants with ROP have an increased risk for other pathologies such as high-level myopia, squint, and cortical brain damage. Therefore, they require a long-term follow-up so that their problems can be appropriately managed.

At each ROP screening session, an ophthalmologist needs to know how to classify the severity of ROP in each eye examined. This classification will provide information about the prognosis and give guidelines for making decisions about screening and treatment. The International Committee for the Classification of ROP has classified it using the following criteria [Figure 2]: (a) The severity of the ROP, (b) The zone in the retina where ROP is found, (c) The extent of the ROP, (d) Whether the retinal blood vessels are dilated and/or tortuous (pre-plus or plus disease) (e) Whether aggressive posterior ROP is present. Furthermore, the severity of ROP is divided into five categories, namely stages 1 – 5.^[58]

4.3.2. Treatment Options for ROP

Background

In ROP Type 1, there is a clear risk of developing blindness, and treatment is indicated. In the case, ROP Type 2, a “wait and watch” approach is indicated. The definition of Type 1 and 2 ROP is as follows:

Type I ROP (high-risk ROP)

- Zone I, any stage ROP with a plus disease or
- Zone I, stage 3, with or without plus disease or
- Zone II, stage 2 or 3 ROP, with plus disease

Type II ROP (low risk)

- Zone I, stage 1 or 2 with no plus disease or
- Zone II, stage 3 with no plus disease

ROP Treatment

The first-line treatment for ROP is laser retinal photocoagulation. This procedure is quite safe if applied properly and can prevent retinal detachment.^[56,57,59,60] In all HIC guidelines, laser treatment is the first treatment; second is intra-vitreous injection with anti-vascular endothelial growth factor (VEGF). This intervention might cause more myopia later, and there is doubt about its safety for disturbed angiogenesis in other (growing) organs. Indonesia's ROP guidelines also place laser treatment as first-line therapy. If the laser is technically not possible to perform (no pupillary response after mydriatics administration), then anti-VEGF is recommended.

The absence of a laser device should not cause delay or cessation of therapy. In this case, the patient should be referred to as soon as the patient is stable enough to be transported to an institution with the facilities and competence for ROP therapy. Laser treatment requires a trained and highly skilled ophthalmologist.^[56,57]

4.4. P (Program, Implementation and Supporting System)

A comprehensive program to reduce the incidence of the devastating disease ROP is needed. Collaborative efforts involving obstetricians, neonatologists, ophthalmologists, nursing staff, and epidemiologists are needed to reduce the incidence of ROP in LMIC caused by the increased survival of VLBW infants, made possible by the increasing number of neonatal intensive care centers.

- A network of regional neonatal intensive care centers with complete facilities is needed. A plan for these centers must be made in consultation with and supported by all stakeholders, including the Government and The Indonesian National Health Insurance System. The program to stop ROP includes prevention, early detection, and screening followed by appropriate therapy to optimize the quality of life of affected newborns.
- All level 3 NICUs should have the adequate materials and knowledge to work according to the STOP-ROP protocol and have access to an ophthalmologist who has the knowledge and materials to screen for ROP – and treatment – if indicated.

Based on the studies on ROP conducted in Indonesia and other literature^[3-5,61,622], we propose the following guideline to prevent and screen preterm infants for ROP. The abbreviation “R1O2P3” is used to facilitate the procedures that must be standard practice in all perinatal/neonatal units [Figure 3].

Figure 3. Diagram/flowchart “How to prevent ROP with STOP-ROP?”

$R_1O_2P_3$

- (R1) After birth, **Resuscitation** is started with room air in a term and late preterm infants. The recommendation for preterm infants of 28 to 32 weeks is 21 to 30% oxygen, below 28 weeks 30%.^[24] Supplemental oxygen is guided by targeted oxygen saturation levels as advised by international resuscitation counsels (2 min 60%, 3 min 70%, 4 min 80%, 5 min 85%).^[27,28]
- (O1). When **Oxygen** is given, use a blender. When oxygen is given, use a transcutaneous saturation monitor. The saturation target should be at 90-92%.
- (O2) Give **Optimal nutrition** and maintain normal glucose levels. Start enteral, preferably mothers' own milk and parenteral nutrition on day one, and give at least 2 g/kg/day amino acids or protein on day one and 3 to 4 g/kg BW/day after that.
- (P1) **Prevent pulmonary injury** by giving early CPAP immediately after birth to infants <32 weeks and surfactant when the infants using CPAP $FiO_2 > 40\%$ despite 10-12 cm H_2O .
- (P2) **Prevent infection** by proper hand hygiene and clean materials and procedures
- (P3) Last but not least, **prevent blood- and exchange transfusion** by restricting blood sampling using micro-lab techniques, prevent anemia and hyperbilirubinemia.

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J. Edy Siswanto had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency Statement J. Edy Siswanto affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Availability Statement The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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CHAPTER 8

General Discussion

Retinopathy of prematurity (ROP), previously known as RetroLental Fibroplasia (RLF), is a severe eye disease seen in newborn infants and mainly in preterm infants. In chapter 1, we give a short overview of the history of this disease as well as a summary of findings on pathophysiology. In short, the disease can resolve -almost completely- by itself, but it can also progress to the blindness of the eye. Well-known risk factors for the development of ROP are -extreme- prematurity and the use of supplemental oxygen. The disease was first noted in the early forties and fifties of the last century when it became clear that preterm infants with respiratory diseases (RDS) could be saved by giving supplemental oxygen. The incidence of the disease declined when the correlation between giving supplemental oxygen and ROP became clear, and the use of oxygen was restricted. A second increase in the incidence of ROP was observed in the last two decades of the past century, when it became possible to keep preterm infants, born after a gestation of 25-29 weeks, alive. The National Population-Based Studies during the last decade in Belgium, Austria, Norway, Australia/New Zealand, Finland, and Sweden in 2009 reported an incidence of any stages of ROP in these infants was 31.8 – 72.7 %, severe ROP 5–34.8%. (1)

A decrease in the incidence of ROP in these tiny infants was observed when new methods became available to prevent and treat RDS and even more when restricted use of oxygen was accepted. A third epidemic of the disease was observed in the last decades, especially in Low/Middle-Income Countries (LMIC) like Indonesia. It became possible, also in these countries, by introducing neonatal intensive care to keep small and sick preterm infants alive. Systems to control the delivery of oxygen, as well as systems to control oxygen levels in the infants, are not always available in LMIC. Therefore, the third epidemic of ROP in the LMIC is most likely due to not well-controlled use of oxygen in newborns in LMIC. The third epidemic began in the 1990s in many countries, like India, China, and countries in South America, Eastern Europe, Russia. The pooled estimate from 13 studies reported the incidence of ROP from 2000 to 2010 was 22% of all survivors <32-wk GA in countries with NMR <5 per thousand births), and 37% (42 studies) in countries with NMR $\geq$ 5. (2) Hardly any data exist for Indonesia. Therefore, we started our

studies on the incidence and potential risk factors for the development of ROP with an inventory of data published so far on the incidence of ROP in Indonesia.

In chapter 2, we describe the incidence of ROP as reported in studies from Indonesia. (3) We identified four papers describing the incidence of ROP in different cohorts. In three studies, infants with a birth weight of less than 1500 g and gestational age of 32 weeks were included; one study included infants up to 37 weeks and a weight of 2500 g. The studies showed a prevalence of all stages ROP from 11.9 and 30.5%. It is difficult to compare these data with the prevalence of ROP found in HIC. First, no details were given in the Indonesian papers regarding the infants' gestational age and no data on mortality. The mortality of very preterm infants is higher in Indonesia than in HIC, suggesting that the incidence found might be an underestimation. Secondly, no data were given on the number of surviving infants that were screened. Due to logistic and financial constraints, not all infants are screened in Indonesia. We also asked centers for the care of blind infants in Indonesia on data about blindness caused by ROP. In these centers, 80 infants with blindness were seen. Forty-eight were born before 28 weeks, 15 between 29-30 weeks, 14 between 31-32 weeks, and three infants were born after 35 weeks. (4) Studies from HIC showed that ROP is mainly seen in infants with a gestational age less than 28 weeks and almost never seen in infants born after 32 weeks or higher. We concluded from these data that the incidence of ROP is most likely higher in infants in Indonesia compared with HIC and that it is also seen in infants with higher gestational ages.

In view of the limitations of the studies described in chapter 2, we analyzed the data on ROP infants admitted to the Harapan Kita Women and Children Hospital, Jakarta, Indonesia, for the period 2005-2015. In this period, 182 infants with a birth weight of less than 1000 gr were admitted. Thirty-seven percent of screened infants showed ROP 1-2, 17% showed severe ROP (3-5). In infants born with a birth weight of 1000-1500 gr, 28% of the screened infants showed ROP grade 1-2, 4% had ROP 3-5. ROP was also seen as infants with a birth weight of more than 1500 gr. The mortality in infants below 1000

gr was 47% and 16% in the group 1000-1500 gr. There was a decreasing trend in mortality in both weight groups, from 80% in the group below 1000 g in 2005 to 15% in 2015. In the group 1000-1500 gr, the mortality decreased in the same period from 33 to 13%. When expressed per gestational age, 19% of screened infants born below 28 weeks showed ROP 1-2, and 21% had ROP 3-5. In the group 28-32 weeks, the incidence of ROP 1-2 was 25% and ROP 3-5 3%. These data are in line with data published from other developing countries. Blencowe et al. estimated the incidence of all stage ROP in infants born after less than 32 weeks in developing countries as nearly 40%. (2) In retrospective cohort studies done from 2009 until 2018, the incidence of ROP in infants below 32 weeks was in Brazil 24% – 34% (5,6), Argentina 26% (8), China 19% (8), and Turkey 27%. (9) This incidence is higher than in developed countries, with an average of 22%. (2) Moreover, the mortality in infants of less than 32 weeks in our data is much higher than in developed countries. In our survey, we found that 38% of infants born <32 weeks died. (10) Recent data from Sweden, England, France, the Netherlands, Canada, and the USA show infants' survival rate less than 32 weeks of 80-90 %. (11-17) In Indonesia, only the healthier very preterm infants will survive. The data as found by us might therefore be an underestimation of the real incidence. ROP is seen more frequently in very sick infants receiving intensive care, including supplemental oxygen. Moreover, also in our population, we found ROP in infants born after a gestational age of more than 32 weeks. This is almost never seen in infants born after this gestational age in developed countries. Although the total number of infants cared for in our hospital is limited, we concluded that the incidence of ROP is higher in Indonesia compared with developed countries and also is seen in infants with higher gestational age. (3)

Studies conducted in developed countries identified risk factors for the development of ROP. As far as we are aware, no study investigated if the high incidence of ROP in Indonesia is related to the same risk factors as in developed countries or that the high incidence might be due to specific factors in developing countries. The main risk factor for ROP found in HIC is a low gestational age and birth weight. Next, the use of supplemental oxygen

is an important risk factor. Many studies demonstrated the relation between the setting of the oxygen saturation monitor and the development of ROP. (18) Setting the monitor at low levels (85%–89%) was related to a lower incidence of ROP but an increased death rate. (19,20) At the same time, setting the monitor between 90%–95% might increase the incidence of ROP. (21) A recent Cochrane Review of five trials including 4965 infants <28weeks' GA targeting the lower levels of SpO₂ (<90%) compared to the higher levels of SpO₂ (>90%) found no significant effect on the composite outcome of death or major disability nor on major disability alone, including blindness. There was, however, an increased average risk of mortality of 28 per 1000 infants treated. (20,22) In 2013 Hellstrom and colleagues published a comprehensive review on the development and risk factors for ROP. (23) They identified the use of oxygen, neonatal hyperglycemia, low levels of insulin-like growth factor, insufficient nutrition, absence of ω -3 long-chain polyunsaturated fatty acids, and late-onset sepsis as risk factors for ROP. So far, there have been no studies evaluating the risk factors for the development of ROP in infants in Indonesia, other than risk factors found in developed countries that might explain the higher incidence of ROP in Indonesia. In chapter 3, we analyzed data from 98 preterm infants with ROP and 77 controls from four NICUs in Indonesia and two eye centers between 2009 and 2014. We found that factors associated with the development of ROP were birth weight (BW), intrauterine growth retardation (IUGR), exchange transfusion, duration of oxygen supplementation, minimum saturation monitor setting, and socio-economic factors. Regarding the progression of ROP, gestational age (GA), being outborn, duration of supplemental oxygen, minimum saturation monitor setting, and socio-economic factors were identified as risk factors.

This study concluded that next to gestational age and birth weight, the use and control of supplemental oxygen are the main risk factors for the development and progression of ROP in preterm infants in Indonesia. Additionally, we confirm that intrauterine growth retardation is a risk factor. Moreover, we found exchange transfusion to be a risk factor, and we found a lower rate of ROP in infants from a lower socio-economic background. Risk

factors for the development of ROP, therefore, seem not to be different for infants in Indonesia compared to developed countries. (24) This indicates that potential options to reduce the incidence of ROP in Indonesia are the prevention of prematurity and strict control of supplemental oxygen delivery.

ROP is a multifactorial disease. Many risk factors have been studied and are associated with ROP development; however, none of the presently identified risk factors can explain why some infants develop ROP while others do not. It is also not known why ROP regresses in most infants and progresses to severe forms in others. Several studies have suggested that genetic factors influence the development and severity of ROP. (25-28) Most studies described an association of mutations in the Norrie disease (ND) gene on the X chromosome with the progression of ROP. (27-33) There might be variations in the presence of mutations among different countries in Asia, as illustrated in the research in Korea and Japan (East Asia), and Kuwait as a Middle Eastern Asian country. (28,32-35) Studies conducted in the Middle East found indications that the incidence of ROP, as well as the progression to severe ROP, might be related to genetic polymorphisms. (35) Studies showed that the mutations of the polymorphisms in the Norrie disease (ND) gene might be related to the progression of ROP. Indonesia is a country with a relatively high incidence of ROP, yet the role of these genetic factors in ROP cases' pathogenesis is still unknown. In chapter 5, we describe a study on the presence of mutations in the ND gene on the X chromosome in infants with both non-advanced and advanced ROP in Indonesia. We included 162 preterm newborn infants. ROP was diagnosed in 83 infants, and 79 infants served as controls. Among those with ROP, 57 infants had ROP type 2, while others had type 1. We did not find any gene polymorphisms in any of the infants with ROP nor the control group. We concluded, therefore, that it is very unlikely that polymorphism in the ND gene contributes to the high incidence of ROP in Indonesia. (36) Still, there are indications that racial differences exist in the development of ROP. (37-38)

In 2009 and 2010, pediatricians-neonatologists and pediatric ophthalmologists in Indonesia came together because they were worried about the high incidence of ROP in their country. As potential causes of the high incidence in Indonesia, they considered the following. First, there might be a lack of awareness of ROP among pediatricians, neonatologists, nurses, and ophthalmologists. Secondly, these health care workers had no good plan on how to prevent this devastating and preventable disease and how and when to screen infants. Finally, there might be financial barriers to screen newborn infants. In order to reduce these problems, the group of neonatologists and pediatric ophthalmologists made a guideline on how to prevent, screen, and treat infants with ROP. This guideline was published in 2010 in the form of a comprehensive guidebook for ROP screening and management. (39) Two years later, it became clear that health care workers did not adhere quite well to the guideline. In order to improve this situation, meetings for both neonatologists and ophthalmologists were held where the guideline was explained in detail. In 2014, health care insurance for all inhabitants of Indonesia was introduced by the government of Indonesia.

The care for -small- preterm infants in Indonesia is provided in hospitals with different levels of care. Level of care increases from local to district hospitals to university and private hospitals and two national referral hospitals. No study so far evaluated if these differences in levels of care result in different mortality rates and differences in the incidence of ROP between the levels of care. We conducted a study as described in chapter 6 to determine mortality and incidence of ROP among the levels of care. (10) We send out questionnaires to 10 government hospitals, eight private hospitals, 14 university-based hospitals, and the two national referral hospitals. In total, 34 questionnaires were sent and received. We asked for data on the number of admissions, the mortality rate, the number of infants screened, and the incidence of ROP, including stages. We asked for the data of 2016 and 2017 to evaluate the effect of the introduction of the guideline and health insurance. We received data on, in total, 12.115 infants with a gestational age <34 weeks. Five thousand two hundred fifty-two infants had a birth weight of less than 1500 g. The overall mortality of infants <34 weeks was

24.1%, 67 % in infants <28 weeks, and 24 % in infants born at 28-32 weeks. Almost 37% of surviving infants were screened for ROP; the incidence of all stage ROP was 6.7%. The incidence of ROP in the group <28 weeks was 18 % of screened infants, of which 4 % severe ROP. In the group 28-32 weeks, the overall incidence of ROP was 7%, of which 1-2 % severe. In the group 32-34 weeks, the mortality was 14% and any stage ROP 4%.

The highest rate of both mortality and ROP was found in the university-based hospitals. The incidence of ROP is much lower compared with both the studies published before and the data we collected in the Harapan Kita Hospital between 2005–2015. At the same time, the figures are still higher than those found in developed countries. Also, ROP is still found in infants with a gestational age of more than 32 weeks. We do not know which factor has contributed most to this decrease in the incidence of ROP, the introduction of the guideline, the meetings held to ask attention to the high incidence of ROP in Indonesia, or the introduction of the national health system. Why the mortality rate and the incidence of ROP were highest in the university-based hospitals cannot be answered from our data. Further studies are needed to determine if the patient population in these hospitals is different from the other hospitals or if other factors might be involved.

Although the incidence of ROP has decreased in Indonesia over the past years, the incidence is still higher compared to developed countries. Continued attention to prevention is essential. In chapter 7, we give an overview of the pathophysiology of ROP, potential risk factors, and methods to prevent ROP. Also, a scheme for screening and treatment is given. This paper might help neonatologists and other health care workers involved in the care for preterm infants to reduce the incidence of ROP in Indonesia.

CHAPTER 9

Summary

Based on our clinical observations and supported by studies done in Low-Middle Income Countries (LMIC) like Indonesia (2, 40), we hypothesized that the incidence of Retinopathy of Prematurity (ROP) in Indonesia is higher compared to High-Income Countries (HIC). The first step to prove our hypothesis was to evaluate papers published on the incidence of ROP in Indonesia. We identified four papers published between 2005 and 2013. The incidence of any stage ROP in infants with a gestational age <32 weeks and/or a birth weight <1500 gram ranges from 11.9-30.5%. (3) Important information needed to compare these data with data from HIC lacked in these papers; there were no data on the number of admissions, mortality rate, and severity of ROP. Still, these data supported our hypothesis that the incidence of ROP is high in Indonesia. In developed countries, ROP is mainly seen in infants with a gestational age <28 weeks and/or birth weight of <1000 gram. (41,42) The mortality of these infants in Indonesia is high, making a comparison between the published data from Indonesia and HIC difficult. In order to relate the incidence of ROP to gestational age and birthweight, we analyzed the data of one of the national referral centers for neonatology in Indonesia, the Harapan Kita Women and Children Hospital, for the period 2005-2015. We found an incidence of ROP of 40% in infants <28 weeks, half of these infants had severe ROP. In the group 28-32 weeks, the total incidence of ROP was 28%, of which 3% severe. ROP was also found in infants with a birthweight >1500 g and a gestational age >32 weeks, while this is hardly seen in HIC. Our data again supported our hypothesis that the incidence of ROP was high in Indonesia. (43)

The most well-known risk factors for the development of ROP are a low gestational age and birth weight, and the use of supplemental oxygen. The third study evaluated if risk factors for the development of ROP in Indonesia were the same or that other risk factors might cause a high incidence of ROP. We found that, in Indonesia, low gestational age and birth weight and the use of supplemental oxygen are the main risk factors for the development of ROP. Efforts to reduce the incidence of ROP, therefore, must be directed to these factors. The care for a pregnant woman in Indonesia is provided by midwives, general practitioners, and obstetricians. There are no guidelines

where a mother, when delivering before 32-34 weeks, should give birth. There are no protocols on transferring pregnant women to a higher level of care in case of complications during pregnancy or potential preterm delivery. Mothers can deliver a -very- preterm infant in all hospitals, also in hospitals where the infrastructure needed for the care of the mother with pregnancy-related complications or the infrastructure for the stabilization and care of preterm infants are not available. Optimal care of the pregnant patient might prolong pregnancy, so preventing -extreme- prematurity. Each week the pregnancy is prolonged, reduces the risk for ROP. (44) Intrauterine growth retardation also is a risk factor for the development of ROP. (24,44) Optimal care of the pregnant mother can help to reduce growth retardation and, thereby, the risk for ROP. The use of supplemental oxygen is an important risk factor for the development of ROP. The strict control of oxygen delivery, both immediately after birth and the period thereafter, is needed. The risk of developing ROP is lower for infants born in a center where the infrastructure needed for preterm infants' care, including systems to control the oxygen supplementation and the infant's resulting oxygen level, are present. (24) Hellström et al. identified in a review additional risk factors for the development of ROP, namely hyperglycemia, low levels of IGF, insufficient nutrition, especially a lack of n-3 long-chain-polyunsaturated acids and late-onset sepsis. (23) Respiratory problems are also risk factors, as they may cause a need for supplemental oxygen. All these risk factors are higher prevalent in sick than in healthier infants. Being born outside a perinatal center increases the risk of these problems and thereby the risk of developing ROP. This again underlines the importance of being born in a perinatal center.

The first step in preventing ROP, therefore, is setting up a system where a pregnant mother with complications during pregnancy, including the risk to deliver <34 weeks, is transferred to a center where optimal care for the mother and the infant is available. In these centers, both well trained personal as well as all equipment needed for the care of a sick newborn infant must be available. The second important issue is the availability of systems controlling the oxygen delivery in all hospitals where newborn

infants are born or admitted and the presence of well-trained personal. Room air must be present because resuscitation of almost all infants can safely be done with room air, while the delivery of oxygen causes free radicals, which are related to the development of ROP. Next, systems to control inspired oxygen concentration and systems to measure the blood's transcutaneous oxygen level are mandatory.

Only approximately half of the infants at risk to develop ROP are presently screened for ROP, despite the presence of clear guidelines on which infants need screening and when. There are several reasons why the rate of screening is low in Indonesia. First, there is a lack of ophthalmologists trained in the screening of preterm infants. Secondly, there are financial barriers. Finally, not all pediatricians might be aware of the importance of screening for ROP, that in some cases, screening and treatment can prevent blindness. The government should be convinced that screening preterm infants for ROP is cost-effective, as cases of blindness might be prevented.

In chapter 7 of this thesis, we combined all recommendations in one scheme with the acronym STOP-ROP. Sending the flyer with this scheme to all places in Indonesia where pregnant mothers are seen, deliveries take place, and newborn infants are cared for is urgently needed. (45)

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Samenvatting

Op basis van onze klinische ervaring en ondersteund door studies uitgevoerd in landen met een Laag/Middel inkomen (LMIC) zoals Indonesië, kwamen wij tot de hypothese dat de incidentie van retinopathie van de prematuur (Retinopathy of Prematurity, ROP) in Indonesië hoger is dan in landen met een hoog inkomen (HIC). Als eerste stap om onze hypothese te bewijzen, analyseerden wij alle publicaties over de incidentie van ROP in Indonesië. Wij vonden vier artikelen die tussen 2005 en 2013 waren gepubliceerd. De incidentie van alle stadia ROP samen bij pasgeborenen met een zwangerschapsduur <32 weken en / of een geboortegewicht <1500 gram varieerde van 11,9 tot 30,5%. Belangrijke informatie nodig om deze gegevens te vergelijken met de incidentie van ROP in HIC ontbraken in deze publicaties. Er waren geen gegevens over het aantal opnames, het sterftecijfer en de ernst van ROP. Toch ondersteunden deze gegevens onze hypothese dat de incidentie van ROP hoger is in Indonesië vergeleken met HIC. In HIC wordt ROP vooral gezien bij zuigelingen met een zwangerschapsduur <28 weken en / of een geboortegewicht <1000 gram. De sterfte van deze pasgeborenen in Indonesië is hoog, waardoor een vergelijking tussen de gepubliceerde gegevens uit Indonesië en HIC moeilijk is. Door de hogere sterfte kunnen gevallen van ROP gemist worden. Om de incidentie van ROP te relateren aan zwangerschapsduur en geboortegewicht, analyseerden we de gegevens van het Harapan Kita Women and Children Hospital, een van de referentiecentra voor neonatologie in Indonesië, voor de periode 2005-2015. We vonden een incidentie van ROP van 40% bij zuigelingen <28 weken, de helft van deze zuigelingen had ernstige ROP. In de groep van 28-32 weken was de totale incidentie van ROP 28%, waarvan 3% ernstig was. ROP werd ook gevonden bij zuigelingen met een geboortegewicht >1500 g en een zwangerschapsduur >32 weken, terwijl dit in HIC nauwelijks wordt gezien. Deze gegevens ondersteunden opnieuw onze hypothese dat de incidentie van ROP hoger is in Indonesië vergeleken met HIC.

De meest bekende risicofactoren voor de ontwikkeling van ROP zijn een korte zwangerschapsduur en laag geboortegewicht en het gebruik van extra zuurstof. In de derde studie werd onderzocht of de risicofactoren voor de ontwikkeling van ROP in Indonesië dezelfde waren of dat andere risicofactoren de hoge incidentie van ROP zouden kunnen verklaren. We vonden dat in Indonesië een korte zwangerschapsduur en laag geboortegewicht en het gebruik van extra zuurstof de belangrijkste risicofactoren zijn voor de ontwikkeling van ROP in Indonesia. Inspanningen om de incidentie van ROP te verminderen, moeten daarom op deze factoren worden gericht. De zorg voor een zwangere vrouw wordt in Indonesië verleend door verloskundigen, huisartsen en gynecologen. Er zijn geen richtlijnen waar een zwangere zou moeten bevallen bij een zwangerschapsduur van minder dan 32-34 weken. Er zijn geen protocollen voor het overbrengen van zwangere vrouwen naar een hoger zorgniveau in geval van complicaties tijdens de zwangerschap of mogelijke vroeggeboorte. Moeders kunnen in alle ziekenhuizen een premature baby ter wereld brengen, ook in ziekenhuizen waar de infrastructuur die nodig is voor de zorg voor de moeder met zwangerschapsgerelateerde complicaties of de infrastructuur voor de stabilisatie en verzorging van premature baby's niet beschikbaar is. Optimale zorg voor de zwangere patiënt kan de zwangerschap verlengen, waardoor extreme prematuriteit wordt voorkomen. Ieder week waarmee de zwangerschaps duur wordt verlengd, vermindert het risico op ROP. Intra-uteriene groeiachterstand is ook een risicofactor voor de ontwikkeling van ROP. Optimale zorg voor de zwangere kan de groeiachterstand helpen verminderen en daarmee het risico op ROP. Het gebruik van extra zuurstof is een belangrijke risicofactor voor de ontwikkeling van ROP. Een strikte controle van de zuurstoftoevoer, zowel direct na de geboorte als de periode daarna, is nodig. Het risico op het ontwikkelen van ROP is lager voor baby's geboren in een centrum waar de infrastructuur aanwezig is die nodig is voor de zorg van premature baby's, inclusief systemen om de zuurstoftoediening te regelen en het resulterende zuurstofniveau van de baby te meten. Hellström et al. publiceerden een

uitvoerig overzicht van alle potentiële risicofactoren voor de ontwikkeling van ROP, namelijk hyperglycemie, lage niveaus van IGF, onvoldoende voeding, vooral een gebrek aan n-3 lange keten meervoudig onverzadigde vetzuren en een sepsis na de eerste levensweek. Ademhalingsproblemen vormen ook risicofactor, aangezien ze gepaard kunnen gaan met de behoefte van extra zuurstof. Al deze risicofactoren komen vaker voor bij zieke dan bij meer gezonde pasgeborenen. Geboren worden buiten een perinataal centrum verhoogt het risico op deze problemen en het risico op het ontwikkelen van ROP. Dit onderstreept nogmaals het belang van geboren worden in een perinataal centrum.

De eerste stap om ROP te voorkomen, is daarom het opzetten van een systeem waarbij een zwangere moeder met complicaties tijdens de zwangerschap, inclusief het risico op bevalling <34 weken, wordt overgebracht naar een centrum waar optimale zorg voor moeder en kind beschikbaar is. In deze centra moet zowel goed opgeleid personeel als alle apparatuur die nodig is voor de verzorging van zieke pasgeborenen beschikbaar zijn. Belangrijk hierbij is de aanwezigheid van apparatuur waarmee de concentratie van de toe te dienen zuurstof geregeld kan worden en apparatuur welke de zuurstof saturatie in het bloed kan meten. Nu wordt, ook in Indonesië, veelal 100% zuurstof gebruikt bij de reanimatie van pasgeborenen. Studies hebben aangetoond dat 100% zuurstof zeer schadelijk is, mede door het verhoogde risico op ROP alsmede schade aan longen en hersenen. Voor de reanimatie van kinderen geboren na een zwangerschapsduur van 32 weken is lucht met een zuurstof concentratie van 21% bijna altijd voldoende, voor kleinere pasgeborenen wordt een mengsel met 30% zuurstof aangeraden. Apparatuur dat de zuurstof concentratie van ingeademde kan meten en regelen alsmede apparaten die transcutaan de zuurstof saturatie in het bloed kunnen meten, is daarom van groot belang.

Slechts ongeveer de helft van de zuigelingen die het risico lopen ROP te ontwikkelen, wordt momenteel in Indonesië gescreend op ROP, ondanks de aanwezigheid van duidelijke richtlijnen over welke zuigelingen gescreend

moeten worden en wanneer. Er zijn verschillende redenen waarom de frequentie van screening in Indonesië laag is. Ten eerste is er een gebrek aan oogartsen die zijn opgeleid in het screenen van premature baby's. Ten tweede zijn er financiële belemmeringen. Ten slotte zijn misschien niet alle kinderartsen zich bewust van het belang van screening op ROP, dat in sommige gevallen screening en behandeling blindheid kan voorkomen. De overheid moet ervan overtuigd worden dat screening van premature zuigelingen voor ROP kosteneffectief is, aangezien blindheid kan worden voorkomen.

In hoofdstuk 7 van dit proefschrift hebben we alle aanbevelingen gecombineerd in één schema met de afkorting STOP-ROP. Het is dringend nodig de flyer met dit schema naar alle plaatsen in Indonesië te sturen waar zwangere moeders worden gezien, bevallingen plaatsvinden en pasgeboren baby's worden verzorgd.

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ematurity, which in the past and until now has not been properly and evenly handled in all areas of Indonesia. Without your patience, enthusiasm, support, and understanding, it would be impossible for me to complete this educational process. Hopefully, this will become an example for the educational attainment of our children in the future.

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I remember that the eight of us were asked one by one to attend, be interviewed and tested regarding the authority of neonatology when I had worked in the unit for 2 full years, so that we could qualify as Pediatrician Neonatologists from AZG / UMCG, Groningen. Before he returned to Holland he gave a certificate to each of us, except for me, he just said *"... Edy, you will get it the same as the others when you return to study from our unit in Groningen"*. With various considerations from our unit, I was only able to fulfill my desire to study after 3 years.

What I remember the most during the joint rounds, he always answers *"... there are two things to think about The first answer is yes and the second is no and the most important next is not yes or no, but what is the reason behind you give that answer."*

As a father, he is very concerned about family life. Even though he knew I was working hard to continue my studies in Groningen, when my second child (Abyasa) was born in Jakarta, he advised me to return to Jakarta to visit my son. He really knows my feelings of not being able to accompany my wife and the birth of the

baby. He gave advice “.... Edy, you better go home, if you want to study neonatology further you can continue by doing research in Jakarta. You can write down your experiences and what you do in your unit. I will help you”

It occurred to me, can I do that? ... Fourteen years on, finally my first international journal was published. This journal was born under his guidance and intervention to reform my raw manuscript at the beginning of my writing. He gave an idea how to dig up a simple thing that we have been working on. The publication of one topic in this journal encouraged me to write a second and subsequent one. I kept in mind, it turns out I can do it too.

In a series of journeys to make paper, I designed a sequential story. There are many things that you teach in overcoming difficulties to publish a paper in a journal. The long journey that must be taken from journal to journal is due to the mismatch of topics or the too high requirement for entry to be published in a very good quality journal. Sometimes it can be boring and frustrating whether a manuscript that we have worked on will be continued or not. It turns out that writing a paper is not as easy as when we trace references to a topic that we want to support the writing of our ideas. So many interesting things from the discussion, comments, appropriate suggestions based on your many experiences which are very helpful in perfecting the manuscript created. Likewise, there are good ways to answer the criticism of the reviewers. Thank you for your patience, always thinking positively, giving praise and appreciating the thoughts of junior doctors like us.

Now after a period, I am here today with the thesis. Even though my performance in this study is not quite perfect, but in the end I have started to move on. I would like to provide input to neonatal services, especially in reducing the incidence of retinopathy of prematurity which can lead to complications of decreased vision ability to blindness. This must be realized by every health worker (general practitioner, pediatrician, neonatologist, ophthalmologist and nurse) and policy makers who are involved in neonatal care.

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journal. This is reflected in the series of meanings that are interwoven in one story, starting from the introduction, the main text and the conclusions that can be drawn from this thesis. Providing ease of registration is a bit hampered, because the program began during the COVID-19 Pandemic era.

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Johanes Edy Siswanto, Jakarta 2021

Curriculum Vitae

Johanes Edy Siswanto was born on November 15th 1964, at Budi Kemuliaan Hospital, Jakarta. He grew up in Jakarta and took his medical education at the University of Indonesia (1983-1989). Just after graduation, he worked as Head of Puskesmas (Primary Health Care) Lewa, Sumba Island, East Nusa Tenggara (1990-1992), an island that carries so many memories, where he as a young doctor was forged to work directly in the community. His excellent work as a doctor at the Public Health Center (Puskesmas) took him to fly to the capital, and he was awarded as the National Model Doctor.

After that, he continued studying Child Health Education at the Department of Pediatrics, Dr. Kariadi Hospital, Faculty of Medicine Diponegoro University, Semarang (1992-1997). After completing the study as a pediatrician, he worked in Berau Regency, East Kalimantan (1997-1999). This district is located on Derawan Island, a quiet fishing village, with its western edge now filled with homestays, bungalows, and wooden piers, as a base for tourist accommodation for diving and snorkeling. In 1999, he returned to Jakarta and started working at RSAB Harapan Kita, the National Center for Women and Child's Health. This hospital is a referral center for high-risk infant patients and various congenital disorders.

From September to December 2003, he received a neonatology scholarship in Groningen, The Netherlands, under Prof. Dr. Pieter J. Sauer Ph.D. and Prof. Dr. Arend F. Bos Ph.D. The motivation given by the two of them to try to start research and writing led him to be interested and deepen the Retinopathy of Prematurity (ROP) problem. This severe retinal disorder can threaten vision and the occurrence of blindness in premature babies. The publication of the first journal through study literature made him even more excited and tried to find solutions on how to reduce the incidence of ROP in Indonesia.

In addition, his daily life in the Neonatology department made him inevitably involved and had to be able to deal with various congenital disorders, which also brought disasters and apparently contributed to the high infant mortality rate in Indonesia. Together with the related team, he tried to put together a treatment program from antenatal care, postnatal emergency, reconstructive surgery to medical rehabilitation so that the affected children can live appropriately in their environment. Together with friends who have the same ideas and passion, he led the establishment of the Birth Defects Integrated Center (BIDIC) at the Harapan Kita Women's and Children's Hospital and has been the chairman since 2013. In addition to that, he is also trusted to coordinate the conjoined twins' separation team in this

hospital. Together with the team, he was also successfully selected to coordinate with professional organizations as well as cross-related programs at the Ministry of Health of the Republic of Indonesia based on the results of the proposal bidding held by WHO-SEARO to design a program to strengthen the prevention and integrated management of Birth Defects in Indonesia.