

RETINOPATHY OF PREMATURITY : CLINICAL CORRELATION
OF THE OCCURRENCE AND SEVERITY WITH RISK FACTORS

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This project is developed to investigate the possible risk factors of retinopathy of prematurity (ROP) occurrence and severity in premature babies who were born in Maharaj Nakorn Chiang Mai Hospital during 1996-1997. We would like to thank with our great appreciation and gratitude to Chiang Mai University for providing financial support and opportunity. Great thanks is given to Assoc. Prof. Dr. Tay Chiengchee, Department of Evaluation and Educational research, Faculty of Education, Chiang Mai University for being the consultance of the project. Further, we would like to thank Miss Kittika Kanjanaratanakorn from Medication Education Section, Faculty of Medicine and Mrs. Soontaree Aupapong from Department of Ophthalmology, Faculty of Medicine, Chiang Mai University for assistance with selecting statistical designs for analyzing our data. We also wish to thank Mrs. Phongphan Uppaphanthawong, headnurse of Neonatal Care Unit (NICU) of Maharaj Nakorn Chiang Mai Hospital who gave us the encouragement and support until this research was finished. A special thanks goes to Department of Pediatrics, and Pediatric Nursing Section and Faculty of Medicine for giving us the opportunity to study this program. Finally, a very special thanks is given to all the babies for being the sample of our study.

RESEARCH TITLE RETINOPATHY OF PREMATURITY : CLINICAL
CORRELATION OF THE OCCURRENCE AND
SEVERITY WITH RISK FACTORS

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Abstract

We have investigated the possible risk factors that may increase the risk of retinopathy of prematurity (ROP) occurrence and severity. The clinical data of 45 premature infants whose birth weight (BW) were equal to or less than 1,250 grams were analyzed. These infants were born in 1996-1997. Data showed the incidence of ROP, 46.67%, and the correlation of gestational age (GA), maximum FiO_2 required and the Apgar score at 5 minutes with the severity of ROP ($P < 0.05$) but they were not correlated with the occurrence of ROP. On the other hand, asphyxia correlated with the occurrence of ROP but not with the severity ($P < 0.05$). Infants with these factors should be considered to have greater risk for either the occurrence or severity of ROP.

เรื่อง Retinopathy of prematurity : ความสัมพันธ์ระหว่างปัจจัยเสี่ยง (Risk factors) กับ การเกิด(Occurrence) และความรุนแรง (Severity) ของโรค

ชื่อผู้เขียน ดาราวรรณ ศิระกมล
ธาดา มาร์ติน

Abstract

ในการศึกษาเพื่อให้ทราบถึง ความสัมพันธ์ของปัจจัยเสี่ยง ที่อาจมีผลต่อการเกิดภาวะ Retinopathy of prematurity (ROP) ในทารกคลอดก่อนกำหนด รวมทั้งที่อาจมีผลต่อความรุนแรงของโรคนี้ ผลจากการศึกษาในทารกคลอดก่อนกำหนดที่มีน้ำหนักแรกเกิดน้อยกว่า หรือเท่ากับ 1,250 กรัม ที่เกิดในโรงพยาบาลมหาราชนครเชียงใหม่ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ในปี พ.ศ. 2539-2540 จำนวน 45 คน พบว่า มีอุบัติการณ์ของการเกิด ROP 46.67 % (21/45) ปัจจัยเสี่ยงที่มีความสัมพันธ์กับการเกิดของ ROP อย่างมีนัยสำคัญทางสถิติ ได้แก่ ภาวะ Asphyxia ($P < .05$) ส่วนปัจจัยเสี่ยงที่มีความสัมพันธ์กับความรุนแรงของโรค อย่างมีนัยสำคัญทางสถิติ ได้แก่ อายุครรภ์ (Gestational age:GA)($P < .05$) , ค่า Apgar score ที่ 5 นาที ($P < .05$) และ Maximum FiO_2 required ($P < .05$) ทารกที่มีความเสี่ยงเหล่านี้ควรได้รับการดูแลเอาใจใส่อย่างตระหนักในอันตรายของภาวะเสี่ยงเหล่านี้ เพื่อลดอัตราการเกิดและความรุนแรงของโรคที่อาจเกิดขึ้นได้

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Chapter 1

Introduction

In presenting 5 year experiences with retinopathy of prematurity (ROP) in Maharaj Nakhorn Chiang Mai (MNCM) hospital, the data obtained indicated that we are experiencing a relative decline in the incidence and severity of ROP¹. Whether this is largely circumstantial or due to better monitoring system in our neonatal unit, is still obscured. One of the notable strategies in our NICU monitoring system was the application of transcutaneous pulse oximeter to all high risk infants receiving oxygen therapy. Despite the meticulous attention to oxygen levels, our 4-year incidence of ROP in premature infants whose birth weight is equal to or less than 1,250 grams is as high as 50.72%.¹ We had earlier reported an incidence of 65.4% in this birth weight stratum in our preliminary report.² Thus, the correlation between blood oxygen levels and ROP occurrence may not be straightforward. Besides, other risk factors in ROP occurrence and severity were still elusive to our knowledge.

We performed a study to determine the correlation between the occurrence and severity of ROP with risk factors that may influence the occurrence and outcome of ROP. The aim of this study is to define statistically significant risk factors that have any effect on the occurrence and severity of ROP in the high risk group. i.e. premature infants whose birth weight is equal to or less than 1,250 grams. We hope to provide better care to these premature babies, along with better understanding of the cause and management of ROP in our hospital.

Chapter 2

Review of Literature

Retinopathy of prematurity (ROP) is a vasoproliferative retinopathy that occurs principally, but not exclusively, in premature infants. It occurs in two somewhat overlapping phases: (1) an acute phase in which normal vasculogenesis is interrupted and a response to injury is observable in the retina and (2) a chronic or late proliferation of membranes into the vitreous during which tractional detachments of the retina, ectopia, and scarring of the macula and significant visual loss occur. More than 90% of cases of acute ROP go on to spontaneous regression, healing with minimal scarring and little or no visual loss. Fewer than 10% of the involved eyes go on to significant cicatrization.

The following is a brief background of ROP. Although not recognized as such, ROP occurred sporadically prior to 1940. During the decade following Terry's initial report, ROP burst onto the consciousness of the pediatric and ophthalmological communities as an epidemic of blindness among premature infants. Silverman estimated that in the decade 1943-1953, 7,000 children in the United States and 10,000 worldwide were blinded by ROP. A hectic, disorganized search for possible causes, ranging from light to lack of iron and vitamins, led nowhere. A pediatrician in Melbourne, Australia, provided the first substantial clinical clue by comparing the frequency of occurrence of ROP in the three nurseries, each differing in the access to supplemental oxygen and noted that each produced different attack rates of ROP. This pointed to a possible etiologic role of oxygen. The study of Patz et al. followed promptly, and supported this conclusion. A randomized prospective trial of oxygen therapy, the Kinsey study, was quickly organized. It was the first application of the then new science of biostatistics in ophthalmology. Its results clearly established that the incidence of ROP was related inversely to birth weight. The study further established that the

incidence of cicatricial retrolental fibroplasia (RLF) (as the end-stage disease was then called) 23% in premature kept for 28 days in an oxygen environment of more than 50 %, and 7 % in infants given oxygen only when clinically necessary and in the condition of less than 50 %. Finally its result seemed to indicate no apparent differences in the mortality and the morbidity between the two groups. There seems to be no relationship between the concentrations of inspired oxygen and ROP. No "safe" level of inspired oxygen was established in this benchmark study, but the conclusion was not based on a formal test : Infants were not assigned to the specified concentrations of oxygen (e.g. 30%, 40%,50%). Shortly before its publication, a single, hospital based, randomized trial was published. This study (which suffered from many a number of design flaws identified in the years that followed) suggested that if oxygen was used in inspired concentration of 40 % or less, the incidence of cicatricial retrolental fibroplasia was zero. Subsequent papers promoted optimistic view, although Kinsey argued to the contrary that no safe level had been established and that oxygen should be given in the lowest concentrations for the shortest duration possible. Having emerged from that decade and from the frightful epidemic, the state of medical knowledge at that time seemed secure : ROP was related causally to birth weight and exposure to oxygen. If oxygen exposure was kept under 40%, the disease disappeared . And so, it seemed, it did.³

Gunn et al. analysed determinant factors that may increase the risk of occurrence of ROP in 80 infants born in 1975 and 1976 with BW 501-1500 grams and found that active and/or cicatricial ROP occurred 33.8 % (27/80) and the factors significantly associated with ROP were GA , apnea requiring bag and mask resuscitation with oxygen , septicemia , degree of illness, blood transfusion , and mechanical ventilation.⁴ Biglan et. al. studied in 1979 -1981 and reported that premature infants who had exposed to increase ambient oxygen with chronic lung disease or chronic lung disease with seizure had a high risk for developing ROP grade 3 (39% and 57% respectively).⁵ Further, Flynn et. al. reported the incidence of ROP in 214 surviving premature infants with BW less than or equal to

1,300 grams that developed 55.6% (119/214) and found that the severity of the disease was strongly correlated with BW and weakly correlated with the total duration of oxygen therapy.⁶ Arroe and Peitersen had studied in the period 1985 - 1991 and reported the significant differences between infants with and without ROP for BW, GA, Apgar score at 1 minutes, resuscitation, ventilator treatment, duration of supplementary oxygen, severe complications in the neonatal period and sequels from the central nervous system. They also found that the occurrence of ROP was related significantly to early intubation, hypotension, persistent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).⁷ Similarly, Tanterdtam et.al. reported in 1993 that BW is the greatest high risk group of ROP, especially those less than 1,250 grams, the incidence was 30.65% (19/62).⁸

DEFINITION OF TERMS

1. Apgar score

: A system (or method), described in 1953, by which condition of the newly-born infant can be assessed for prognosis and the need for particularly close observation or care in the delivery room and nursery. The Apgar method of scoring is of practical value at 1 and 5 min. The score taken at 1 min is an index of asphyxia and of the need for assisted ventilation; the 5 min score is a more accurate index of likelihood of death or neurological residual. A score of 0,1,2 is given in each of 5 variables - heart rate, respiratory effort, muscle tone, reflex irritability and color. The maximum score is 10 and the minimum is 0. In this study Apgar score at 5 min was selected because it's more accurate index of likelihood of death or neurological residual.

2. Asphyxia

: An inability to breath , resulting from obstruction to airflow at the mouth , nose (or other parts of respiratory tract). In this study we confirmed the condition of asphyxia with Apgar score at 5 min at the score of equal to or less than 7 or by the pediatrician physical examination.

3. Birth Weight (BW)

: The body weight measured at birth (gram). In this study we selected the premature infants whose BW were equal to or less than 1,250 grams.

4. Gestational Age (GA)

: The period of the condition from conception to delivery of the conceptus (week). In this study we selected the premature infants whose GA were less than 37 weeks.

5. Premature infant

: An infant born before the appointed time . In this study we selected 45 infants born in Maharaj Nakorn Chiang Mai in 1996-1997 whose BW were equal to or less than 1,250 grams and GA were less than 37 weeks.

6. Severity of ROP

: A grade of ROP that has been classified by ICROP¹⁰ into 3 categories, 1) staging 2) extent 3) location . In this study we selected " staging " to represent the severity of ROP that can be classified into 5 stages , stage 1-5. The least is stage 1 and the most is stage 5 . Stage 0 means no ROP.

Chapter 3

Materials and Methods

Study population :

All premature infants born at the MNCM hospital whose birth weight is equal to or less than 1,250 grams were eligible to this study. This stratum was selected because the incidence of ROP is higher than other strata.

Sample size :

Our incidence in this high risk group is 50.72 %¹. It was necessary to enroll 45 premature infants which would result in 100 percent of confidence. The sample size calculation was done by Taro Yamane formula.⁹

Examination method :

Fundus examinations were performed on all infants by an ophthalmologist using binocular indirect ophthalmoscope and scleral depressor. Further, details of the examination method were outlined elsewhere.² The examination were performed 6 to 8 weeks after birth. They were repeated every one or two weeks until the infants were discharged from the hospital. The fundus findings were recorded by retinal drawings and the ROP was characterized by using the International Classification of ROP (ICROP).¹⁰

Protocol :

The hospital records of all infants were reviewed and the following data collected : Birth weight (BW) , Gestational age (GA) , Sex, asphyxia , Apgar score at 5 minutes , apnea of prematurity, intraventricular hemorrhage, septicemia, blood transfusion, persistence ductus arteriosus, mode of oxygen therapy, maximum FiO_2 required (inspired oxygen concentration) , duration of supplementary oxygen , duration of hospitalization., etc. (as shown in table 2)

Statistics :

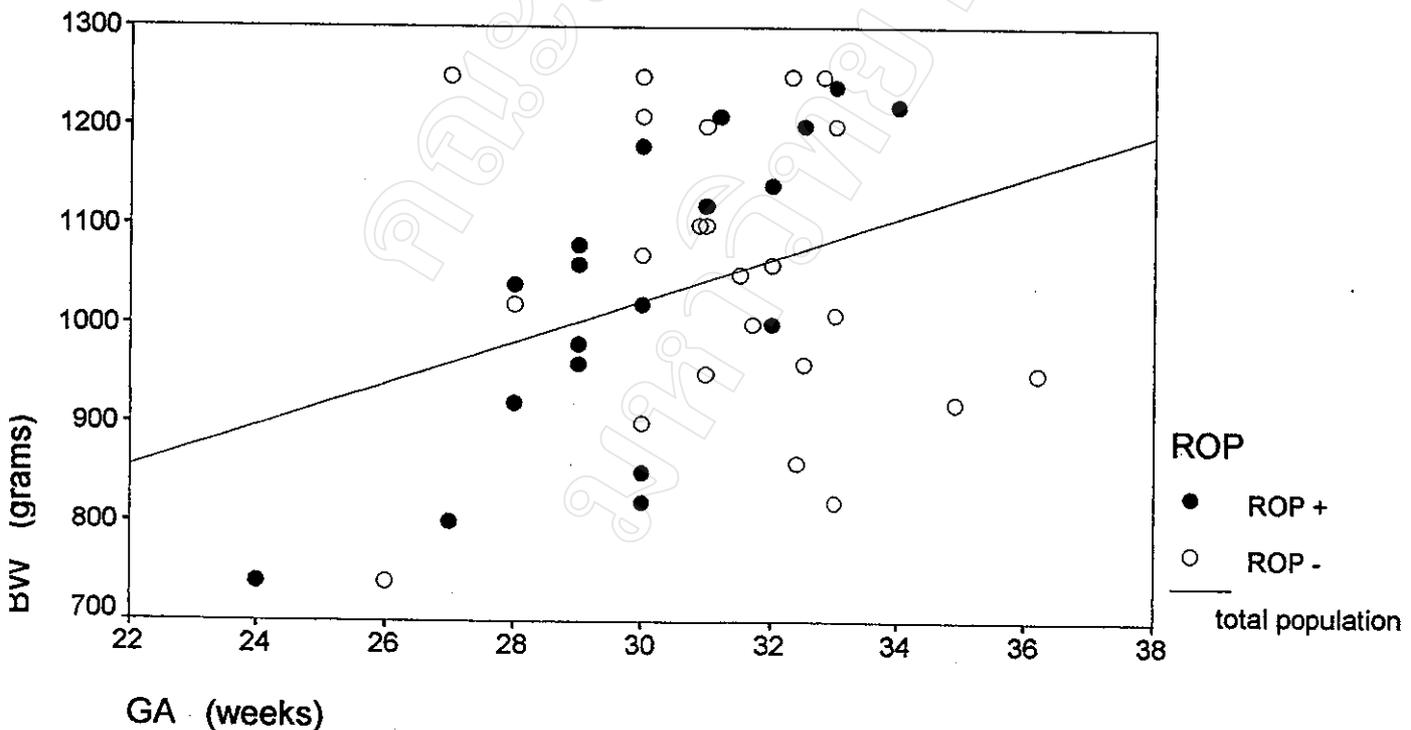
Infants with ROP (ROP+) were compared without ROP (ROP-) using both χ^2 (Chi-square test) and a correlation analysis with calculation of Spearman' rank correlation coefficient. The p value for the entry of the variables into the model was $P < 0.05$. The severity of ROP was scored by using the number of ROP staging as a score i.e. 0 means no ROP and 5 represents most severe ROP. The score of 3 to 5 is considered as severe ROP.

Chapter 4

Results of the study

In the study population ROP was detected in 21 of 45 infants (46.67%). Severity exceeding stage 3 was not found. Relationship between BW and GA of the ROP+ and ROP- group are demonstrated in the scatter plot in figure 1. Statistically compared, GA was found to be correlated with severity of ROP ($P=0.013$). Of the parameters in oxygen therapy that were compared between the two groups, birth asphyxia related significantly with ROP occurrence ($P=0.028$). When tested for correlation, asphyxia does not correlate with severity of ROP.

Figure 1 Scatter plot of relationship between GA and BW in ROP + and ROP -



Statistical analyses of the maximum FiO_2 and the Apgar score at 5 minutes demonstrated a correlation with the severity of ROP ($P=0.010$ and $P=0.044$ respectively). Records of variables are summarized in table 1.

Table 1 Recorded data of the ROP+ and ROP- groups that demonstrate relation to either occurrence or severity of ROP. Values are number of infants or mean values.

variable	ROP+	ROP-	occurrence		severity	
			correlation coeff.	p value	correlation coeff.	p value
GA(week) (mean \pm SD)	29.89 ± 2.23	31.30 ± 2.26	.559**	.367	-.3668*	.013
BW(gram) (mean \pm SD)	1019.5 ± 150.7	1051.7 ± 147.2	.592**	.562	-.1578*	.300
asphyxia	12	6	.327**	.028	.343**	.1110
Apgar score at 5 minutes (mean \pm SD)	7.05 \pm 2.50	8.50 \pm 1.61	.460**	.148	-.3016*	.044
max. FiO_2 (%) (mean \pm SD)	78.33 \pm 28.61	55.29 \pm 34.11	.489**	.167	.3810*	.010

* Spearman' rank correlation coefficient

** Chi - square test

เลขทะเบียน.....เลขหมู่.....
สำนักหอสมุด มหาวิทยาลัยเชียงใหม่

Table 2 Clinical data in premature infants who did or did not have ROP

Risk factors	ROP(n=21)	no ROP (n=24)	Correlation coef.**	p value
Birth weight (gram) *	1019.5±150.7	1051.7±147.2	.592	.562
Gestational age (week) *	29.89±2.23	31.30±2.26	.559	.367
Sex (M/F)	9/12	10/14	.012	.936
Small for Gestational age (SGA)	7	5	-.202	.175
Apnea of prematurity	12	9	.149	.316
Asphyxia	12	6	<u>.327</u>	<u>.028</u>
Apgar score at 5 min *	7.05±2.5	8.5±1.61	.460	.148
BPD(Bronchopulmonary Dysplasia)	11	8	.192	.197
RDS (Respiratory distress syndrome)	13	8	.286	.055
IVH (Intraventricular Hemorrhage)	4	3	-.047	.751
PDA (Patent ductus arteriosus)	11	8	.239	.109
Sepsis	6	6	.040	.787
Pneumonia	5	5	.036	.811
Duration of hospitalization (day) *	70.5±29.9	58.4±22.6	.634	.554
Duration of caring in NICU *	25.1±19.2	15.4±15.5	.648	.253
Duration of receiving oxygen therapy *	23.1±18.3	17.2±16.6	.630	.434
Duration of requiring ventilator *	14.9±15.8	9.2±11.0	.574	.390
Duration of receiving I.V. fluid *	17.0±10.2	11.7±10.6	.522	.610
Dura. of receiving parenteral nutrition *	6.7±10.8	3.3±7.0	.469	.519
maximum FiO ₂ required *	78.33±28.61	55.29±34.11	.489	.167
Receiving blood transfusion	12	10	.107	.472
On ventilator	19	16	.285	.055
Number of blood transfusion *	1.33 ± 1.8	1.42 ± 2.1	.266	.843
NICU case	19	16	.285	.055

** Chi - square test

* mean value ± SD

Chapter 5

Discussion and Conclusion

The total number of all premature infants being examined during 1996-97 was 159. There were 45 infants that had BW less than or equal to 1,250 grams. Of these 21 developed ROP. It is generally accepted that BW was proved to be a single most important factor in ROP. Many studies suggest that birth weight, gestational age, and duration of oxygen exposure are the most significant factors associated with ROP development.¹¹⁻¹⁴ Feilder et. al. found that in premature babies weighed less than 1400 grams , the best predictor for developing severe ROP was BW.¹⁵ Shohat et . al. reported in 1983 that there were no significant differences between the 34 infants with ROP and the 31 infants who did not develop ROP in mean BW or mean GA.¹⁶ Although contradicting opinions existed , it is generally taking into account that the incidence of ROP in the low birth weight especially those equal to or less than 1,250 grams is unquestionably higher than other groups. This generally accepted incidence is exemplified in our data as shown in table 3.

Table 3 Incidence of ROP in each birth weight strata.

BW(gram)	n	ROP+	incidence(%)
501-1250	45	21	46.67
1251-1500	51	7	13.70
1501-1750	45	4	8.90
≥ 1751	18	1	5.60

GA was evaluated by either Dubowitz' score or Ballard' score or the date of the last menstrual period. We found it's difficult to verify the date taken as LMP

in some cases. This control scheme difficulty could affect the exact estimation of GA. Statistical analyses of the mean GA in ROP+ and ROP- group are shown in table 1.

In this study we do not find a different risk of ROP development in both groups regarding to GA but in the ROP+ group there was a statistical significant correlation between GA and severity ($P = .013$).

One issue of interest in ROP is whether perinatal respiratory distress is a risk factor or not . Phelps suggested that an early acute injury to immature retinal vessels occurred right after birth and this started ROP.¹⁷ In our study, statistical analyses of asphyxia and Apgar score at 5 minutes showed a significant relation of birth asphyxia to ROP occurrence but no correlation to severity. On the other hand , Apgar score at 5 minutes was correlated to ROP severity but not with the occurrence. The findings seems to indicate that pulmonary function right after birth is a factor in ROP.

Oxygen therapy had been most extensively investigated in ROP. No clear relationship could be established between intermittently sampled PaO₂ and ROP. Study on cutaneous monitoring of PaO₂ by Flynn suggested that there were factors other than PaO₂ that are most important in development of ROP.¹⁸ The assumption that in an immature hypoxic retina a vaso-proliferating substance is released , a factor X as called by Michaelson in 1950s , is still elusive to researchers now.¹⁹ We found a correlation of maximum FiO₂ and severity of ROP.

Recently, Phelps and Gaynon postulated that the O₂ concentration level during the recovery period of the prethreshold ROP is critical to the progression of ROP.^{17,20} If the O₂ level is lower in ROP during the recovery period this would significantly affect the outcome of ROP. They suggested a high level of O₂ supplementation (96-100%) during this period in order to reduce the progression of ROP to advanced stage.

Other risk factors being investigated by us are receiving of blood transfusion , patent ductus arteriosus(PDA), duration of receiving oxygen therapy , sepsis, apnea of prematurity, intraventricular hemorrhage, respiratory distress

syndrome(RDS), duration of receiving parenteral nutrition, duration of requiring ventilator, etc.(as shown in table 2). We do not find these factors significantly related to ROP occurrence and severity.

Conclusion

We would conclude that on clinical aspect BW is a predictor for ROP, GA has a correlation with severity. Premature infants with low BW and poor pulmonary function at birth ,signified by birth asphyxia and low Apgar score at 5 minutes are at higher risk for ROP development and severity. The concept of early injury to the immature retina vessel at birth and this could be one of the factor that cause ROP. The practice of limiting oxygen in infants with prethreshold ROP is being challenged by high concentration of supplemental oxygen concentration during the recovery period as suggested by Phelps and Gaynon.

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