Evaluation of the outcomes and regression rate after early treatment for Retinopathy of Prematurity treatment in King Chulalongkorn Memorial Hospital

Mr. Yothin Titawattanakul

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การประเมินผลลัพธ์และอัตราการถดถอยภายหลังการรักษาโรคจอประสาทตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นในโรงพยาบาลจุฬาลงกรณ์

นายโยธิน ฐิตวัฒนกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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By	Mr. Yothin Titawattanakul
Field of Study	Clinical Sciences
Thesis Advisor	KITTISAK KULVICHIT, M.D.
Thesis Co Advisor	ADISAI VARADISAI, M.D.
	Apivat Mavichak, M.D.

Accepted by the Faculty of Medicine, Chulalongkorn University in Partial Fulfillment of the Requirement for the Master of Science

..... Dean of the Faculty of Medicine

(Professor SUTTIPONG WACHARASINDHU, M.D.)

THESIS COMMITTEE

..... Chairman

(Prasart Laksanapuk, M.D.)

..... Thesis Advisor

(KITTISAK KULVICHIT, M.D.)

..... Thesis Co-Advisor

(ADISAI VARADISAI, M.D.)

..... Thesis Co-Advisor

(Apivat Mavichak, M.D.)

..... External Examiner

(Assistant Professor Navapol Kanchanaranya, M.D.)

โยธิน ฐิตวัฒนกุล : การประเมินผลลัพธ์และอัตราการถดถอยภายหลังการรักษาโรคจอประสาทตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นในโรงพยาบาลจุฬาลงกรณ์ . (Evaluation of the outcomes and regression rate after early treatment for Retinopathy of Prematurity treatment in King Chulalongkorn Memorial Hospital) อ.ที่ปรึกษาหลัก : นพ.กิตติศักดิ์ กุลวิชิต, อ.ที่ปรึกษาร่วม : นพ.อดิศัย วราดิศัย,นพ.อภิวัฒน์ มาวิจักขณ์

-วัตถุประสงค์หลัก: เพื่อศึกษาผลลัพธ์ที่ไม่พึงประสงค์และประเมินอัตราการถดถอยภายหลังการรักษาโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นในโรงพยาบาลจุฬาลงกรณ์

-วัตถุประสงค์รอง: เพื่อศึกษาภาวะแทรกซ้อน และประเมินการเพิ่มมากขึ้นและการกลับเป็นซ้ำของโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดภายหลังการรักษาโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นในโรงพยาบาลจุฬาลงกรณ์ รวมทั้งเพื่อระบุปัจจัยเสี่ยงสำหรับการเกิดโรคจอประสาทตาในทารกคลอดก่อนกำหนด

-รูปแบบงานวิจัย: การศึกษาเชิงพรรณนาแบบย้อนหลังและการศึกษาจากเหตุไปหาผลแบบย้อนหลัง

-ผู้เข้าร่วมงานวิจัย: ทารกที่คลอดก่อนกำหนดทุกรายที่ได้รับการตรวจคัดกรองโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่เดือนมกราคม 2552 ถึงมกราคม 2557

-วิธีการศึกษา: ข้อมูลรวบรวมมาจากเวชระเบียนผู้ป่วยในและผู้ป่วยนอกของทารกที่ได้รับการตรวจคัดกรองโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดที่คลินิกโรคจอตาผิดปกติในทารกคลอดก่อนกำหนด , หออภิบาลผู้ป่วยทารกแรกเกิดระยะวิกฤต และหออภิบาลผู้ป่วยทารกคลอดก่อนกำหนด ตั้งแต่เดือนมกราคม 2552 ถึงมกราคม 2557 ที่โรงพยาบาลจุฬาลงกรณ์ โดยที่ข้อมูลที่ทำการรวบรวมจะแบ่งออกเป็น 4 ส่วน ได้แก่ ข้อมูลทั่วไป, ประวัติการฝากครรภ์ของมารดา และภาวะแทรกซ้อนปริกำเนิดและหลังคลอด, ข้อมูลที่เกี่ยวข้องกับโรคจอตาผิดปกติในทารกคลอดก่อน, ผลสืบเนื่องและผลลัพธ์ภายหลังการรักษา โดยทำการเปรียบเทียบผลลัพธ์ที่ไม่พึงประสงค์, อัตราการถดถอย, ภาวะแทรกซ้อน, การเพิ่มมากขึ้นและการกลับเป็นซ้ำภายหลังการรักษาระหว่างกลุ่มที่ให้การรักษาโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้น (โรคระยะที่ 3 อยู่ในบริเวณใดของจอตา และมีหรือไม่มีลักษณะเส้นเลือดที่คดงอหรือขยาย ซึ่งไม่เข้ากับระยะprethreshold ประเภท 1) กับกลุ่มให้การรักษาตามมาตรฐานของโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดในปัจจุบัน (ระยะprethreshold ประเภท 1) และวิเคราะห์ปัจจัยเสี่ยงของมารดาและทารกที่สัมพันธ์กับการเกิดโรคจอตาผิดปกติในทารกคลอดก่อนกำหนด

- ผลการศึกษา: ผลลัพธ์ที่ไม่พึงประสงค์หลังจากการรักษาพบ 6 ตาจาก 28 ตา (21.43%) ในกลุ่ม prethreshold ประเภท 1 แต่ไม่พบผลลัพธ์ที่ไม่พึงประสงค์ในกลุ่มที่ได้รับการรักษาตั้งแต่ต้นที่มีจำนวน 63 ตา อย่างมีนัยสำคัญทางสถิติ (P=0.001) ในกลุ่มที่ได้รับการรักษาตั้งแต่ต้นรักษาด้วยเลเซอร์ LIO จำนวน 63 ตา พบอัตราการถดถอยของโรคภายหลังการรักษา 100% ในขณะที่กลุ่ม prethreshold ประเภท 1 ROP จำนวน 26 ตาที่ได้รับการรักษาด้วยเลเซอร์ LIO พบอัตราการถดถอยของโรคภายหลังการรักษา 88.46% (23 ตา) และ 11.54% ที่ไม่พบการถดถอยของโรค (3 ตา) และทารกคลอดก่อนกำหนด 1 คนที่ตาทั้งสองข้างได้รับการรักษาด้วยการผสมผสานระหว่างเลเซอร์ LIO และการฉีดยา Bevacizumab เข้าวุ้นตา พบว่าไม่มีการถดถอยของโรคภายหลังการรักษา การเกิดขึ้นซ้ำของเส้นเลือดงอกใหม่ (neovascularization) และจะต้องได้รับการรักษาซ้ำเกิดขึ้นจำนวน 2 ตา (7.14%) ในกลุ่ม prethreshold ประเภท 1 แต่จะไม่พบการเกิดขึ้นซ้ำของเส้นเลือดงอกใหม่ในกลุ่มที่ได้รับการรักษาในตั้งแต่ต้นแต่อย่างไม่มีนัยสำคัญทางสถิติ (P=0.092) การเพิ่มมากขึ้นของโรคภายหลังการรักษาพบจำนวน 3 ตา (10.71%) ในกลุ่ม prethreshold ประเภท 1 แต่ไม่พบการเพิ่มมากขึ้นของโรคในกลุ่มที่ได้รับการรักษาตั้งแต่ต้นอย่างมีนัยสำคัญทางสถิติ (P=0.027) สำหรับปัจจัยที่ส่งผลต่อการเกิดโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดอย่างมีนัยสำคัญ ได้แก่ น้ำหนักและอายุครรภ์ของทารก และภาวะเลือดออกในโพรงสมอง

- สรุปผลการศึกษา: การรักษาโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นขั้นต้นในโรงพยาบาลจุฬาลงกรณ์สามารถลดผลลัพธ์ที่ไม่พึงประสงค์และเพิ่มอัตราการถดถอยของโรคภายหลังการรักษาเมื่อเปรียบเทียบกับการรักษาตามมาตรฐานของโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดในปัจจุบัน (ระยะprethreshold ประเภท 1)อย่างมีนัยสำคัญ ยิ่งไปกว่านั้นการรักษารักษาโรคจอตาผิดปกติในทารกคลอดก่อนกำหนดตั้งแต่ต้นยังสามารถลดการเกิดซ้ำและความเพิ่มขึ้นของโรคหลังการรักษาและมีภาวะแทรกซ้อนจากการักษาที่ต่ำ

สาขาวิชา	เวชศาสตร์คลินิก	ลายมือชื่อนิสิต .....
ปีการศึกษา	2562	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....
		ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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KEYWORD: Retinopathy of prematurity, Early treatment for retinopathy of prematurity, Outcomes, Regression rate

Yothin Titawattanakul : Evaluation of the outcomes and regression rate after early treatment for Retinopathy of Prematurity treatment in King Chulalongkorn Memorial Hospital. Advisor: KITTISAK KULVICHIT, M.D. Co-advisor: ADISAI VARADISAI, M.D., Apivat Mavichak, M.D.

- Primary objectives: To study the unfavorable outcomes and assess the regression rate after early treatment protocol for the ROP in KCMH.

- Secondary objectives: To study the complications and evaluate the progression and recurrence of ROP requiring retreatment after early treatment protocol for the ROP in KCMH. To identify the independent risk factor for the Retinopathy of Prematurity development in KCMH.

- Design: The Retrospective descriptive study and retrospective cohort study.

- Participants: The study included all premature infants who were screened ROP in King Chulalongkorn Memorial Hospital from January 2009 to January 2014.

- Method: The data retrieved from the medical records (IPD & OPD) of all infants who screened for ROP at ROP clinic, NICU and prematurity unit from January 2009 to January 2014 at King Chulalongkorn Memorial Hospital (KCMH). The data were collected 4 parts: general data, ANC data and peri-/post- natal complication, ROP associated data, Sequelae and outcomes. The maternal and infant risks data use to analyse the association of ROP development between ROP group and no ROP group. The early treatment protocol for the ROP treatment in KCMH group (the stage 3 ROP in any zone and any plus and could not be compatible with prethreshold type 1 ROP and threshold ROP) was compare the unfavorable outcomes, regression rate, complications, progression and recurrence of ROP with the previous standard treatment (Prethreshold type 1 ROP) in KCMH group.

- Main Outcome and Measures: The unfavorable outcomes and the regression rate after the early treatment protocol for ROP.

- Result: The unfavorable outcomes after ROP treatment in KCMH occur 6 eyes from 28 eyes (21.43%) in the prethreshold type 1 ROP group but no unfavorable outcomes in the early treatment protocol group (63 eyes). There were statistically significant in difference between 2 groups (P=0.001).The early treatment protocol group in KCMH who treated with laser LIO (63 eyes) found 100 % of regression rate after the treatment, while the prethreshold type 1 ROP among 26 eyes were treated with laser LIO found 88.46 % of regression rate (23 eyes) and 11.54 % of non-regression (3 eyes). There were 2 eyes from 1 preterm infant who was treated with combination between laser LIO and IVT Bevacizumab found that that the non-regression after treatment was 100%. The recurrence of neovascularization after regression ROP and requiring re-treatment occur in 2 eyes (7.14%) of the prethreshold type 1 ROP group, but no recurrence in the early treatment group. There were not statistically significant in difference between 2 groups (P=0.092). The progression after ROP treatment without regression ROP occur 3 eyes (10.71%) in the prethreshold type 1 ROP group, but no progression in the early treatment group. There were statistically significant in difference between 2 groups (P=0.027). Bodyweights (BW), IVH and gestational ages (GA) were significantly associated with ROP development.

- Conclusion: The early treatment protocol for the ROP in KCMH significantly reduced the unfavorable outcomes and increased the regression rate when compare with the previous standard early treatment of Retinopathy of Prematurity in the prethreshold type 1 ROP. Moreover, the early treatment protocol for Retinopathy of Prematurity in KCMH significantly reduced the recurrence and progression after treatment with the low complications.

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2019	Advisor's Signature .....
		Co-advisor's Signature .....
		Co-advisor's Signature .....

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Yothin Titawattanakul

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CHAPTER 1

INTRODUCTION

1.1 RATIONAL

Retinopathy of prematurity (ROP) is the causes of blindness and severe visual impairment worldwide in premature (preterm) infants. The ROP is the important cause of blindness of the children in the middle-income countries including China, India, Vietnam and Thailand. WHO defined the premature (preterm) infants as the babies born alive before 37 weeks of pregnancy. The sub-categories of preterm infant based on gestational age (GA) can be divided into extremely preterm (less than 28 weeks), very preterm (from 28 to 32 weeks), moderate to late preterm (from 32 to 37 weeks). Approximately 15 million infants in each year are preterm birth and this number is rising globally [1]. The preterm birth complications are the cause of death among children less than 5 years old and approximately 1 million children die because of that complication in 2015 [2]. More than 80 % of preterm infants are born between 32 and 37 weeks of gestation age (moderate to late preterm) and many infants of this group die needlessly because lacking of necessary cares and supports [1]. About 10% of preterm infants, who are born between 28 and less than 32 weeks of gestation age in the low-income countries, have died more than half of this group [1]. The survival of preterm infants have the multiple disabilities such as learning disabilities, hearing and visual problems. The ROP has the immature retinal vasculature of the immature retina with the extent of the immature retina area, which depending mainly on the degree of prematurity at birth of infants. The retina of infant has no blood vessels until the 16 weeks of gestation age and the retina vasculature proceeds in-utero from the optic nerve head begins during 14-15 weeks of gestation

age, then the vascular reaches the nasal ora serrata at 36 weeks of gestation age and temporal ora serrata at 39-41 weeks of gestation age to complete the mature vascular of retina. Normally, the retina and retinal vasculature are completely developed in the almost term infants so the development of ROP does not occur. On the other hand, the preterm infants have the incomplete development of the retina and retina vasculature at birth that leading to develop ROP at 4-6 weeks after birth. The preterm infants or infants who have the associated neonatal morbidity such as respiratory distress syndrome, severe systemic illness, infection, poor weight gain, and hyperglycemia are increased the risk of ROP development [3]. The incidence of ROP is increasing in the global populations because of the advance of neonatal medical care, therefore the improvement of survival rate of premature infants tended to be increasing the risk of ROP occurrence in the future. As a result, ROP becomes the important ocular problem in preterm infants of the public health worldwide. Moreover, the ROP problem is the one of the greatest challenges in less developed countries for having an adequate screening by the ophthalmologists, who have been experienced in the examination for diagnose ROP with indirect ophthalmoscopy and have a good judging for management [4]. The effective screening and treatment requires the proper time for retinal examinations according to the infant's gestational age at birth and the disease severity because there is a small window of opportunity for the effectively examination of the retina and the time for ROP treatments. The effective examination and treatment improve the visual outcome and prevent the blindness. The most cases (approximately 90%) of ROP infants are mild severity that can spontaneously resolve without requiring any treatment. The small proportions of ROP infants progress to severe ROP. If the severe ROP cases are untreated, that can be result of retinal detachment, traction, distortion of the retina and scarring. The finally, the disease is usually become an irreversible severe vision impairment and

blindness. The most important aspect of the ROP is the preventable and treatable disease by early and proper time for screening and appropriated treatments.

Average 13.0 million (12.7–14.3 million) of 15.0 million preterm born infants are estimated to have survived after the one month of life. At least 184,700 (169,600–214,500) infants were found ROP and 53,800 infants progressed to potent visual impairment and required the treatment, but only 22,700 (42%) of these groups received the treatment [3]. The American Association of Pediatric Ophthalmology and Strabismus (AAPOS) reports about 14,000 newborns per year were affected by ROP in the United States [4]. Derived data from the schools for the blindness and blindness prevalence estimate at least 50,000 children aged up to 15 years are blind from ROP globally, with the highest proportion in South America [3]. The data from Childhood Blindness subcommittee, LA IAPB found that there are globally estimated 60,000 children who are blind from ROP, while the largest number about 25,000 children are in the South America region. From the data, the blindness due to ROP tends to increase in India and China because their economies improve and the neonatal intensive care services are expanded [5]. Approximately 2 million infants are birth weight < 2000 grams and 26 million annual live births have the risk of ROP development in India [6]. The incidence of ROP in India is about 38-51.9% in the low birth weight infants [6, 7]. The incidence is very high as 80-100% in the preterm infants with weight less than 900 grams at birth and gestational age of less than 25 weeks [7]. From 26 million annual live births in India, approximately 2 million are birth weight < 2000 grams and have a risk of developing ROP. In 2010, the recent global burden of disease estimated 257,000 years lived with disability globally. The disability associated with visual impairment secondary to ROP [3]. An estimated 32,300 (24,800–44,500) preterm survivors in 2010 had long-term visual impairment by ROP. The severe visual impairment or blindness groups had about 20,000

(15,500–27,200) children. The mild or moderate visual impairment groups had about 12,300 (8,300–18,400) children. However, only 6.2% (1,400–2,900) of the visual impairment group were born in 32–36 weeks of gestational age. About 16% of survivors born at gestational age < 32 weeks were estimated to have some degree of ROP and 3% had a visual impairment in 2010 worldwide [3]. The highest total preterm births at risk of ROP in East, Southeast Asia and Pacific had about 292,500 preterm infants. The infants of this group developed any stage of ROP about 64,000 preterm infants and they had severe visual impairment or blindness from ROP about 7,500 preterm infants (the percentage of total by region was 2.6%). Following by Latin America and Caribbean had 133,300 preterm infants, the infants in this group developed any stage of ROP 29,300 preterm infants and there were severe visual impairment or blindness 3,500 infants (2.6%). South Asia had 79,600 preterm infants, the infants in this group developed any stage of ROP 16,800 preterm infants and there were severe visual impairment or blindness 2,300 infants (2.6%). North Africa and Middle East had 82,200 preterm infants, the infants in this group developed any stage of ROP 18,100 preterm infants and there were severe visual impairment or blindness 2,200 infants (2.8%), Eastern Europe and central Asia had 79,100 preterm infants, the infants in this group developed any stage of ROP 17,200 preterm infants and there were severe visual impairment or blindness 2,000 infants (2.5%), Sub-Saharan Africa had 31,200 preterm infants, the infants in this group developed any stage of ROP 6,700 preterm infants and there were severe visual impairment or blindness 900 infants (2.58%). On the other hand, the high income countries had the least number of total preterm births at risk of ROP and there were severe visual impairment or blindness from ROP 1,700 infants (1.1%). In Thailand, there were found the incidence of ROP about 3,402 infants per year [8]. Approximately 0.1% of the blinding children in Thailand were caused by ROP.

Nowadays, the ROP is the greatest burden of disease in the rapidly developing economies, including India, China, South America, South East Asia and Thailand.

Table 1 The estimated number of preterm births at risk of ROP, developing ROP, severity of ROP, and visual impairment from ROP by region in 2010

	East and Southeast Asia and Pacific	Latin America and Caribbean	South Asia	North Africa and Middle East	Eastern Europe and Central Asia	High income	Sub-Saharan Africa	Total
Number of preterm births receiving neonatal intensive care at the risk of ROP in 2010	292,500	133,300	79,600	82,800	79,100	149,000	31,200	848,300
Number of preterm infants developing any ROP	64,000	29,300	16,800	18,100	17,200	32,700	6,700	184,700
Number of preterm infants developing Pre-threshold type 1 ROP requiring treatment	19,900	9,300	5,300	5,700	5,200	6,300	2,100	53,800
Number of preterm infants with severe visual impairment or blindness from ROP	7,500	3,500	2,200	2,200	2,000	1,700	900	20,000
Number of preterm infants with mild and moderate visual impairment or blindness from ROP	1,100	2,000	900	1,200	1,100	2,300	400	12,300

About VISION 2020 is a global initiative of the International Agency for the Prevention of Blindness. They have a mission for the elimination of avoidable blindness by the year 2020. The one of key elements VISION 2020 is the strategies for the control of the major blinding eye diseases, including the blindness in children so the blindness from ROP is recognized as a priority for control in Latin America, Eastern Europe, and urban areas of Asia [5]. The target of WHO VISION 2020 is controlling the prevalence of blindness worldwide to be less than 0.5% in the all countries within 2020. The epidemiology of blindness and low vision in the Thai children found 0.11% in the prevalence of blindness and 0.21% in the prevalence of low vision. The number of blindness and low vision in Thai children were 13,101

cases and 26,670 cases. The major causes of blindness in Thai children were retinopathy of prematurity (ROP) 66.67% and following by amblyopia from uncorrected high myopia (≥-9.00 diopter in both eye) 33.33%. The major causes of low vision in Thai children were amblyopia from uncorrected high myopia (range between -6.00 and -11.00 diopter in both eye) 28.55% and following by cortical blindness, congenital cataract, optic atrophy, corneal disorders and congenital nystagmus 14.29% [9]. In India had among 1,100 – 1,500 infants annually, who developed the severe ROP with requiring the treatment. About 400-600 newborns became legal blindness from ROP [7]. Over 60% of birth weight less than 1251 grams infants in United Kingdom developed ROP. Approximately 94% of these infants had the mild ROP that do not require treatment. There were only 6% of these infants with severe ROP and requiring the treatment [10]. The ROP is the disease that affected the quality of life of the patient, especially the preterm infants who had a birth weight less than 2000 grams. The ROP has very important socioeconomic impact, so the ROP is the important problems in public health and become the leading cause of childhood blindness throughout the world. However, the ROP can be preventable visual impairment when health personnel are early proper detection and treatment.

Retinopathy of prematurity (ROP) is a disease of abnormal retinal vascular development in prematurity. The major risks are low birth weight infants and low gestational age (GA) infants. The distribution of preterm births by GA was based on a meta-analysis of 131 million live births [9]. The study data showed 5.2% (95% confidence interval (CI: 5.1–5.3%) were less than 28 weeks, 10.4% (95% CI: 10.3–10.5%) were 28–31 weeks, and 84.3% (95% CI: 84.1–84.5%) were at 32–36 weeks. The global prevalence of low birth weight infants, who were GA <28 weeks, had approximately 0.8 million (0.7–0.9 million), GA 28–31 weeks had 1.6 million (1.5–1.7

million), and 32–36 weeks had 12.6 million (12.3–14.0 million) [11]. The data from the Canadian Neonatal Network found that approximately 40-50% of the infants, who born before 31 weeks of GA, could develop any stage of ROP, 7-8% of the infants could develop severe ROP and 5-6% of the infants required the treatment [12]. In summary, the ROP affects the retina of preterm infants. The incompletely vascularized of immature retina cause the local ischemia with subsequent retinal neovascularization development, and then the fibrovascular proliferation occurs. In the end stage of the disease develop the retinal detachment and that is the cause of blindness in the ROP infant. The ROP screening and proper management are the keys to success for the best visual and anatomical outcomes in the ROP infants.

About the ROP screening must be done at the proper time, thus a setting of screening criteria is the most importance. The examination should be appropriated in order to balance the infant's safety and the all necessary means to saving the infant's vision. The goals of an effective ROP screening must be to identify the risk preterm infants, who could be useful for the treatment and make appropriate on the timing of ROP screening and take a proper treatment. The guidelines for screening and treatment of ROP are different in each country. The American Academy of Pediatrics (AAP) and The American Academy of Ophthalmology (AAO) recommend for screening in the infants with a birth weight of ≤ 1500 grams, gestational age of 30 weeks or less and selected infants with a birth weight between 1500 and 2000 grams or gestational age of > 30 weeks with an unstable clinical course such as requiring cardiorespiratory support or who are believed by their attending pediatrician or neonatologist to be at high risk for ROP [4]. The AAP and AAO recommend for screening is similar to the Royal College of Ophthalmologists of Thailand recommendation screening in the infants with a birth weight of ≤ 1500 grams or gestational age of 30 weeks or less or selected infants with a birth weight

between 1500 and 2000 grams or gestational age of >30 weeks with an unstable clinical course (systemic illness, who are believed by their attending pediatrician or neonatologist to be at high risk for ROP) [13]. The screening ROP in King Chulalongkorn Memorial Hospital based on the decision making of the pediatrician or neonatologist to be the high risk for ROP. The department of ophthalmology and department of pediatrics at King Chulalongkorn Memorial Hospital had a joint agreement for screening and treatment for ROP that base on the guidelines worldwide and the Royal College of Ophthalmologists of Thailand recommendation. The researcher collects the data in the screening and treatment of ROP infants in order to collect the information on relationships among the preterm infants with the ROP.

About the results of treatment for ROP, there were not the specific treatment for ROP in the past. Until 1988, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study suggested the treatment for the threshold ROP with cryotherapy, ablated the peripheral avascular retina. The result of the study found that the reduction of unfavourable outcome about 50% (the unfavourable outcome had 21.8% in the treatment group compared with 43.0% in the control group). However, the outcomes of treated patient have been frequently poor. The poor anatomic outcome is the cause of the poor vision after the long term follow up. A recent report from CRYO-ROP study found that when the children were 15 years old, almost half of the treated eye (44%) had visual acuity of 6/60 or worse in despite of their improved retinal outcomes after treatment [14]. Afterwards, the benefits of earlier treatment of ROP infants were studied in the Multicenter Early Treatment for Retinopathy of Prematurity (ETROP) study in late 2003. This study was randomly allocated to the early laser treatment group (the high risk prethreshold disease) compared with the delayed treatment group (the threshold disease development and the regressed eyes without

treatment were observed). In this study considered the treatment for the cases of prethreshold type 1 ROP disease (the high risk prethreshold disease). The treatment in this group had significant benefit to the early treated eyes when compared with the delayed treated eyes. The outcome demonstrated reduction in unfavorable visual acuity outcomes (from 19.5% to 14.5%, P = 0.01) and unfavorable structural outcomes in the early treatment group (from 15.6% to 9.1%, P < 0.001) [15]. When the researcher analyzed from the previous studies, we found that the earlier treatment for ROP get better both the structural and visual outcomes. In the earlier treatment of ROP infants in the ETROP study, the results still found some unfavorable visual and structural outcomes in the early treatment groups. The progression of the prethreshold type 2 ROP to the prethreshold type 1 ROP in ETROP study had about 22.1%. About 11.5% of the prethreshold type 2 ROP progressed to the prethreshold type 1 ROP in less than 7 days [16]. The past 10 years has been used anti vascular endothelial growth factor (VEGF) agents for the treatment of ROP infants such as Bevacizumab (Avastin). For the management of ROP infants in King Chulalongkorn Memorial Hospital was earlier treated of ROP infants than the previous studies. We treated all infants who had stage 3 ROP in any zone and any plus including stage 3 ROP with incompatible with the prethreshold type 1 ROP and the threshold ROP. The results of the previous studies still found the progression of ROP and the development of unfavorable visual and structural outcomes in the early treatment group of the study. Moreover, the treatments of ROP in King Chulalongkorn Memorial Hospital were applied in multimodality treatments for the best outcomes such as used conventional laser therapy or combined conventional laser therapy with intravitreal Bevacizumab. Therefore, in this research, we need to evaluate the unfavorable outcomes and the regression rate after the early treatment protocol of the ROP in King Chulalongkorn Memorial Hospital and subgroup analysis in

comparison between the early treatment protocol for the ROP in King Chulalongkorn Memorial Hospital and the standard treatment group (the threshold ROP and prethreshold type 1 ROP) as well. Including, in this research study the complication after treatment and evaluate the recurrence and progression after treatment and identify the associated risk factors with the ROP development.

1.2 OBJECTIVES

1.2.1 Primary objectives

1. To study the unfavorable outcomes after early treatment protocol for the Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

2. To assess the regression rate after early treatment protocol for the Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

1.2.2 Secondary objectives

1. To study the complications and sequelae after early treatment protocol for the Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

2. To evaluate recurrence of ROP requiring retreatment and progression after early treatment protocol for the Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

3. To identify the independent risk factor for the Retinopathy of Prematurity development in King Chulalongkorn Memorial Hospital.

1.3 RESEARCH QUESTION

How different about the unfavorable outcome and the regression rate after early treatment protocol in all stage 3 ROP with incompatible with the prethreshold type 1 ROP and the threshold ROP in King Chulalongkorn Memorial Hospital when compared with the previous standard treatment studies (the threshold ROP and prethreshold type 1 ROP) ?

1.4 HYPOTHESIS

The early treatment protocol for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital are decrease the unfavorable outcomes and increase the regression rate of ROP treatment when compare with the previous standard study (the threshold ROP and prethreshold type 1 ROP).

1.5 VARIABLE

1.5.1 Independent variable: The multimodality treatments for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital

1.5.2 Dependent variable: The unfavorable outcomes, the regression of ROP, the recurrence of ROP requiring retreatment, the progression after treatment and the complication & sequelae after treatment

1.6 DEFINITIONS

1.6.1 The early treatment protocol for the Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital was defined as the preterm infants are stage 3 ROP in any zone, any plus and could not be incompatible with the prethreshold type 1 ROP and the threshold ROP

1.6.2 Unfavorable outcomes was defined as

1. Posterior retinal fold involving the macula
2. Retinal detachment involving the macula
3. Retrolental tissue or “mass” obscuring the view of the posterior pole

1.6.3 Regression of ROP was defined as

The medical record noted the regressed of ROP in the record that can imply to a physician, who examined infant, was certain about the improvement of the disease. The improvement of ROP could refer to

1. The retinal vessel growth into retinal avascular area
2. Decrease of the height and width of intraretinal ridge

3. Regression of neovascularization

Regression rate after early treatment protocol for ROP was calculated from the ratio of the regression of ROP infants who followed up until by 54 weeks' postmenstrual to the total of ROP infants who received the treatments.

1.6.4 Progression of ROP was defined as increasing neovascularization after treatment or progress to retinal detachment

1.6.5 Recurrence of ROP was defined as recurrence of neovascularization after regressed ROP and requiring additional treatment

1.7 SCOPE OF STUDY

This research is study of the unfavorable outcome and the regression rate after early treatment protocol for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital and compare the results after early treatment protocol with the standard treatment. The researcher performs a retrospective medical records review of all infants who were screened and treated ROP at our institution from January 2009 to January 2014. The results after treatment of ROP were recorded.

1.8 EXPECTED OR ANTICIPATED BENEFIT GAIN

1.8.1 The results of the study can be further applied as reference for treatment guidelines for Retinopathy of Prematurity treatment in Thailand.

1.8.2 Getting the information about complications and sequelae after treatment for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

CHAPTER 2

REVIEW OF RELATED LITERATURE AND RESEARCH

A study on evaluation of the outcomes and the regression rate after the early treatment protocol for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital. The researcher reviewed the textbooks and related literature for this study. The contents cover the following topics:

2.1 RETIONOPATHY OF PREMATURITY (ROP)

2.1.1 Normal retinal vasculature and development

1. Vasculogenesis
2. Angiogenesis

2.1.2 Pathogenesis

1. The Flynn's hypothesis
2. The role of oxygen
3. The role of light

2.1.3 The international classification of Retinopathy of prematurity (ICROP)

1. The location of retinal involvement by zone
2. The extension of retinal involvement by clock hour
3. The staging or severity of the disease
4. Plus and Pre-plus disease
5. Aggressive posterior retinopathy of prematurity (AP-ROP)
6. Regression of ROP

2.2 WORLDWIDE ROP SCREENING FOR PRETERM INFANTS AND FOLLOW UP EXAMINATION

2.2.1 The American Academy of Pediatrics (AAP) and The American Academy of Ophthalmology (AAO) recommend for screening ROP and follow up examination

2.2.2 The Canadian Pediatric Society (CPS) recommend for screening ROP and follow up examination

2.2.3 The guidelines for ROP screening and treatment in Latin American Countries

2.2.4 The guideline for screening of retinopathy of prematurity in South Africa

2.2.5 UK Retinopathy of Prematurity Guideline

2.2.6 The new guidelines for ROP screening in Sweden

2.2.7 Screening for Retinopathy of prematurity in New Zealand

2.2.8 Retinopathy of prematurity screening criteria in Iran: new screening guidelines

2.2.9 The National Neonatology Forum of India (NNF) Clinical Practice Guidelines for Retinopathy of prematurity

2.2.10 The clinical practices guidelines for Retinopathy of prematurity in Malaysia

2.2.11 The recommended Philippines guideline for screening and referral of Retinopathy of prematurity (ROP)

2.2.12 The Royal College of Ophthalmologists of Thailand recommendation

2.3 TREATMENT OF RETINOPATHY OF PREMATURITY (ROP)

2.3.1 Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study

2.3.2 The Early Treatment for Retinopathy of Prematurity (ETROP) study

2.3.3 The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP)

2.1 RETIONOPATHY OF PREMATURITY (ROP)

Retinopathy of prematurity (ROP) is a disease of abnormal retinal vascular development in premature. First, the disease was described by Terry in 1942 [17]. Terry's reported the condition retrolental fibroplasia (RLF), which involved the proliferation of embryonic hyaloid and developed the retinal detachment behind the lens. Owens and Owens found that the hyaloid system was normal at birth, and then

the retrolental fibroplasia developed postnatally. The pathogenesis of the disease became more understood, then the term of Retinopathy of prematurity (ROP) was adopted. The major risks of ROP are low birth weight (BW) and low gestational age (GA) of infants. The incidence of ROP development related to the birth weight and gestational age in many studies: The CRYO-ROP study found that the ROP develop in 65.8% of infants who weigh less than 1250 grams at birth, 81.6% of infants who had a birth weight of 1000 grams, 60% of infants who born at GA 28-37 weeks, 80% of infants who born less than GA 28 weeks [14]. The Early Treatment for Retinopathy of prematurity (ETROP) Study found that the ROP develop in 68% of infants weighing less than 1251 grams at birth, 44% of infants with a birth weight of 1000-1250 grams, 76% of infants with a birth weight of 750-999 grams, 93% of infants with a birth weight of 750 grams or less [15]. The gestation-specific risk of any ROP by neonatal mortality rates group (NMR) used the population-based incidence of ROP from 2000 to 2010 founded that 21.8% (95% CI: 16.6–27.0%) of all survivors who had GA <32 weeks in countries with NMR < 5, and 36.5% (95% CI: 31.8–41.4%; 42 studies) in countries with NMR ≥ 5 developed some degree of ROP [3]. There are multiple associated risk factors of ROP, including oxygen supplemental therapy, blood transfusions, apnea, hypercapnia, sepsis, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia. The associated risks contributes to the development of ROP. The abnormal changes in ROP development are as a result of immaturity, systemic illness, relative hyperoxia of the extrauterine environment, maternal risks and etc. Po-Mai Lui et al. (2005) studied the risk factors of ROP in preterm infants who weigh less than 1600 grams. The 6 significant variable factors were as follows: birth weight less than 1000 grams, intraventricular hemorrhage, sepsis, use of glucocorticoid or dopamine. These were the risk factors associated with higher incidence of ROP development [18]. A Danish National Study

(2016): Neonatal Risk Factors for Treatment Demanding Retinopathy of Prematurity found that only the blood transfusion and mechanical ventilation were new statistically independent risk factors to predict the development of demanding treatment ROP. In this study included 6,490 premature infants who were born in Denmark from 1997 to 2008 [19].

2.1.1 Normal retinal vasculature and development

The normal retinal vascularization development begins during GA 16 weeks from the mesenchymal tissue, the blood vessel precursor, containing the spindle cells, that is the source of retinal vessels formation. The normal retinal vascularization proceeds in-utero from the disc margin (at 16 weeks of gestation) through the nerve fiber layer to periphery and completely reaches the ora serrata nasally (at 36 weeks of gestation), and then reaches the ora serrata temporally (at 39-41 weeks of gestation). The vascularization results from 2 processes. These processes are different in time, location, and visual prognosis:

1. Vasculogenesis: the formation of new vessels by transformation of vascular precursor cells. The vessels proceed from the optic nerve to periphery, begins during 14-15 weeks PMA. The vascular endothelial growth factor (VEGF) not be role in this process. (Characteristics of zone I disease)
2. Angiogenesis: the budding from the existing vessels progress rapidly in 25 weeks PMA. The capillaries were developed in this process. The vascular endothelial growth factor (VEGF) stimulates endothelial angiogenesis. (Characteristics zone II disease)

2.1.2 Pathogenesis

1. The Flynn's hypothesis from the clinical and histopathological observation to hypothesis of the sequence of develop the ROP. The following sequence are the events in human ROP pathogenesis [20].
2. Endothelial injury occurs at the site, where has differentiated from mesenchymal cells to form the primitive capillary meshwork. From the animal studies, the short duration of hyperoxia resulted in the capillary damage and the most recently differentiated vascular complexes restriction. There are the environmental factors apart from the oxygen involved ROP such as nitric oxide, that can contribute to the vaso-obliterative stage of ROP. While, the reducing of VEGF may result in the endothelial cells death because it is the role as a survival factor of endothelial cells.
    a. The mesenchymal cells of the mature arteries and veins survival are merged via the remaining vascular channels to form the mesenchymal arteriovenous shunt after the vascular endothelial injury. The arteriovenous shunt replaces the death or damaged capillary bed.
    b. The mesenchymal arteriovenous shunts are located at the demarcation area between the avascular and vascularized retina. There are the nest of primitive mesenchymal cells and maturing endothelial cells, which are fed by mature arteries and veins. This shunt area not have the capillaries. Flynn suggested that this structure represents the pathognomonic lesion of acute ROP.

Flynn showed that the cells inside the shunt divide and differentiate to the normal capillary endothelium. They form the primitive endothelial tubes, then the brush border of capillaries grows anteriorly into the avascular retina area. This process represents the ROP involution, which he observed the capillary growth occur in more than 90% of cases at the early stage. When the disease progress, the primitive cells inside the shunt proliferate and grow through the internal limiting membrane and grow up into the vitreous gel. The proliferation growth of new vessels lack of the differentiation and destructive the proliferation of cells. The proliferation vessel invade into the spaces and tissues. The process of membrane proliferation lead to the traction retinal detachment.

3. The role of oxygen

About the role of oxygen, the oxygenation could help to improve the survival of preterm infants. From the previous study found that the supplement oxygen was major cause of ROP. Chan – Ling T et al. (1995) studied about the mechanism of oxygen effects on the immature retina: The primary stage, the relatively hyperoxia of the extrauterine environment after the birth lead to decrease the vascular endothelial growth factor (VEGF), insulin-like growth factor -1 (IGF-1) that resulting in suppressed normal vessel development and vaso-obliteration occurrence. The secondary stage, the non-perfused peripheral retina at 31-34 weeks PCA becomes hypoxic phase from the metabolic demand. The hypoxia lead to increase the vascular endothelial growth factor (VEGF), insulin-like growth factor -1 (IGF-1), that result in the retinal neovascularization and sequelae complication [21]. Many study explained the mechanism of oxygen's effect on the immature retina. The immature retinal vascular of preterm expose to the high concentration of oxygen. The oxygen contribute to vasoconstriction of major vessel and follow by vaso-obliteration of the capillary bed, that cause relatively hypoxia of the peripheral retina. In the

experimental study of the young kittens: The first stage (retinal vasoconstriction and vascular occlusion), the vasoconstriction occurs within several minutes after oxygen exposure. The initial of this stage, a vascular diameter is reduced by approximately 50%, and then its rebounds to original dimensions. If the oxygen exposes continuously, the retinal vasculature will gradually vasospasm during the next 4–6 hours. This process has been occurred until approximately 80% of the retinal vasculature constriction [22]. The process of this stage can be reversible, but the arterial oxygen partial pressure is persistently elevated for 10–15 hours, and then some immature peripheral vessels are permanently occluded. This process can progress depend on the duration of hyperoxia exposure. The vascular occlusion is complete obliteration after 2–3 days of exposure. The most of capillaries are lost and only the major retinal vessels survive. The second stage (retinal neovascularization), the up-regulation of local VEGF-A is playing a key role in the pathologic of retinal angiogenesis. The angiogenic factor (VEGF) is released, and then the neovascularization and fibroglial proliferation are occurred, that lead to tractional retinal detachment. In the experimental study in young kittens found that the marked endothelial proliferation arises from the residual vascular complexes adjacent to retinal capillaries, when transfer the animal to ambient air following sustained hyperoxia. The nodular proliferation of the endothelial cells form the new retinal vessels. The new retinal vessels grow both within the retina and through the internal limiting membrane to its surface, that similar to the neovascularization. The preretinal neovascularization develop the tented membranes, that are the cause of the tractional retinal detachment [20].

By the early 1970s, the arterial blood gas analysis was wildly used for caring the preterm infants. The oxygen requirements of premature infants with respiratory distress syndrome were known. There was a study found that the ROP was not

related to the arterial oxygen levels, but the duration of exposure was related to ROP development [22]. There are two trials in Australia and the United Kingdom for comparison with 2 preterm infant groups (the lower (85% to 89%) oxygen-saturation range and the higher (91% to 95%) oxygen-saturation range). The results are non-significantly higher rates of death or disability between the 2 groups at 2 years of the study [23]. The role of supplemental therapeutic oxygen for the prethreshold ROP (STOP-ROP) was studied in 1999 [24]. In the study enrolled the preterm infants who confirmed the prethreshold ROP in at least 1 eye and median pulse oximetry < 94% saturation were randomized to a conventional oxygen with pulse oximetry at 89% to 94% saturation or a supplement with pulse oximetry at 96% to 99% saturation, for at least 2 weeks. The study enrolled 649 preterm infants from 30 centers. There were randomized 325 infants in conventional oxygen group and 324 infants in supplement group. The rate of progression to threshold ROP was 48% in conventional oxygen group and 41% in supplemental group. The structural outcomes of infants were showed similarly of severe sequelae in the both groups (Retinal detachment or fold (4.4% in conventional oxygen group VS 4.1% in supplement group) and macular ectopia (3.9% in conventional oxygen group VS 3.9% in supplement group)). In conclusion, using of supplemental oxygen did not cause further progression of the prethreshold ROP. Using of raising the oxygen saturation did not make worsening of ROP, but it was not clear benefit for ROP.

4. The role of light

The Light Reduction in Retinopathy of Prematurity (Light-ROP trial) is the prospective multicenter randomized controlled trial study of the effects of light reduction. There are 409 preterm infants with birth weights of less than 1251 grams and gestational ages of less than 31 weeks [25]. 205 preterm infants were exposed to reduced light with the light-blocking goggle, by reduced within 24 hours after

birth. The goggles reduce the visible-light exposure by 97 percent and ultraviolet-light exposure by 100 percent. The other group 204 preterm infants took the typical nursery lighting. The reduced light with the goggle group, the infants wore the goggles until 31 weeks' postconceptional age or 4 weeks after birth, whichever was longer. When the goggles were removed, the ophthalmologists assessed the infants for ROP at least biweekly for up to 13 weeks. The mean ambient-light level adjacent to the infants' faces were measured 399 lux for the goggles group and 447 lux for the control group. The ROP was diagnosed in 102 infants (54%) in the reduced light with goggles group and 100 infants (58%) in the control group (relative risk, 0.9; 95 percent confidence interval, 0.8 to 1.1; P = 0.50). In conclusion the light reduction in ambient-light exposure did not alter the incidence of ROP.

As explained earlier, the term infants have completely vascularized retina, therefore they are not risk for developing ROP. On the other hand, the premature infants have incompletely vascularized retina, so the immature retina area is absent retinal vascularalization. The retinal ischemia occur and lead to release of the vascular growth factors, including vascular endothelial growth factor (VEGF), erythropoietin, insulin-like growth factor-1 (IGF-1), then the neovascularization develops that area. The neovascularization are fragile and leaky, scarring and pulling the retina. The tractional retinal detachment can occur, when the disease progresses. The end stage of disease is complete tractional retinal detachment and maybe occur the fibrovascular plaque behind the lens. The retinal detachment is the most common cause of the visual impairment and blindness in ROP.

2.1.3 The International Classification of ROP (ICROP)

The International Classification of ROP (ICROP) was first published in 2 parts, the first in 1984 and later expanded in 1987, and then was revised in 2005 [26]. That was a consensus statement of an international group of retinopathy of prematurity

experts. The original ICROP dealt with the early phases of ROP, that was based on several observations in order to describe the retinopathy. These classifications could describe the disease, including: (1) the location of retinal involvement by zone, (2) the extent of retinal involvement by clock hour, (3) the stage or severity of retinopathy at the junction of the vascularized and avascular retina, and (4) the presence or absence of dilated and tortuous posterior pole vessels (plus disease) and guiding the treatment (cryotherapy or laser, or observation).

1. The location of the disease: The retina area is divided into 3 zones (center on the optic nerve)

- Zone I (posterior pole) - the posterior pole or inner zone. It is a circle with radius of 30°, centered on the optic disc, whose radius is twice the distance from the optic disc to the macula.
- Zone II - from edge of zone I point tangential to nasal ora serrata (at the 3 o'clock position in the right eye and the 9 o'clock position in the left eye) and temporally. This imaginary boundary corresponds approximately to the anatomic equator.
- Zone III - remaining temporal crescent of retina anterior to zone II, which is the farthest from the optic disc. This is the last zone to become vascularized.

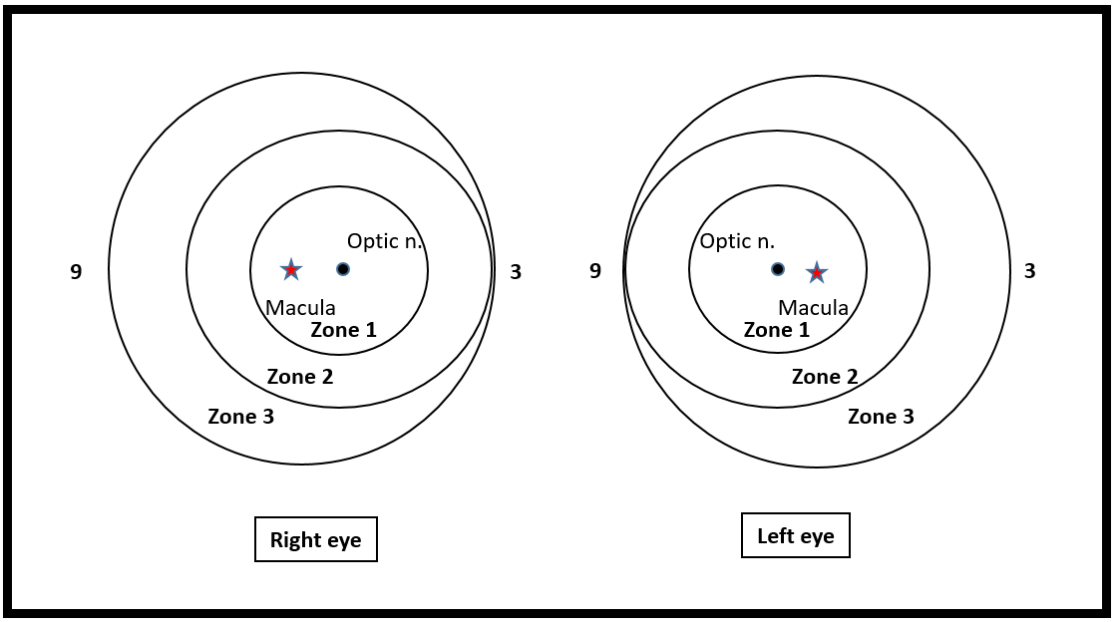

Figure 1 The retina showing zone borders and clock hours use to describe the location and extent of ROP.

An approach by using a 25- or 28-diopter (D) to approximate temporal extent of the zone I, that can be determined. Placing the nasal edge of the optic disc at one edge of the field of view, the limit of zone I is at the temporal field of view. Any ROP must be identified the fall into 1 of 2 posterior zone. The ophthalmologists must be sure the vessels reach the nasal ora serrata and there is not ROP development before recategorizing of the eye as zone III.

2. The extension of the disease: that is the number of clock-hours or as 30° sectors were involved. As the examiner looks at each eye of an infant, the 3 o'clock position is to the right and nasal in the right eye and temporal in the left eye, and the 9 o'clock position is to the left and temporal in the right eye and nasal in the left eye.

3. The severity of the disease: It can be called the staging of ROP. The severity can be divided into 5 stages. The stages are used to describe the abnormal vascular response at the junction of vascular-avascular area.

- Stage 1 - A demarcation line: Separating the avascular retina (anterior) from the vascularized retina (posterior). Characteristic is the flat, white and lies within the plane of the retina. The abnormal branching of retinal vessels leads up to the line. The vascular changes can be dilatation rather than tapering of the peripheral retinal vessels before develops the demarcation line, but these changes are insufficient for the diagnosis of ROP. Either progressing to stage 2 or turn to normal vascularization within several weeks.

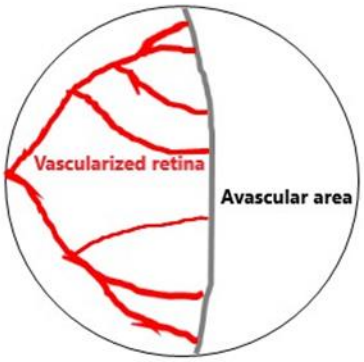

Figure 2 The picture demonstrate a demarcation line at the junction between vascular and avascular area.

- Stage 2 - A ridge with height and width (the hallmark of stage 2 ROP): The demarcation line of stage 1 has grown in height and width. It occupies a volume and extends centripetally. A ridge color may be white or pink. A ridge area has a small tufts of new vessels (“popcorn” lesions), that may be located posteriorly on the ridge. The temporal border of vascular and avascular retina may be triangular shape (“V sign”). In this stage, the lesion is absence constitute the degree of fibrovascular growth and no leakage of fluorescein on angiography, this characteristic can find in stage 3.

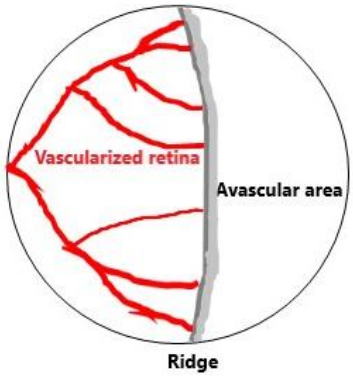

Figure 3 The picture shows a ridge at the junction between vascular and avascular area.

- Stage 3 – A ridge with extraretinal fibrovascular proliferation: This proliferating of extraretinal fibrovascular tissue or neovascularization is localized continuous with the posterior and interior aspect of the ridge. The exraretinal fibrovascular tissue cause a ragged appearance of the ridge, when this proliferation is increasing into the vitreous. The severity of stage 3 lesion can be described to mild, moderate and severe, depending on the extension of extraretinal fibrovascular infiltrate into the vitreous.

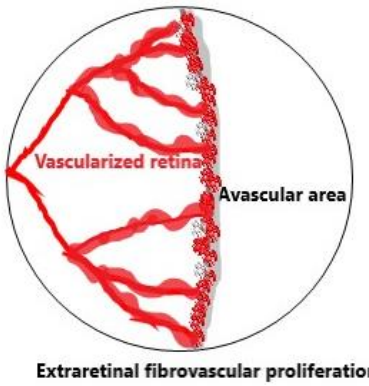

Figure 4 The picture shows ROP with ridge with extraretinal fibrovascular proliferation (Neovascularization) above the ridge extended to vitreous cavity. The posterior pole vessels show increased tortuosity and dilatation.

- Stage 4 – Subtotal retinal detachment: Characterized by the presence of a partial, but a definite retinal detachment. The most common of the retinal

detachment is tractional in nature, but occasionally there are some exudative effusion fluid, or traction, or both.

- Stage 4 A - Extrafoveal retinal detachment: Typical characteristic is a concave and occurs in the periphery retina without involvement of the central macula. The location occurs at the sites of extraretinal fibrovascular proliferation and there is the vitreous traction. The retinal detachment begins at the point of fibrovascular attachment to the vascular retina. The detachment may extend to 360 degrees, segmental or occupying only a portion of the periphery. The prognosis of anatomical and visual are relatively good in the absence of posterior extension. The retinal reattachment is frequently spontaneously resolve and not affect the macula function.
- Stage 4B - Partial retinal detachment including the fovea: This stage can follow the extension of stage 4A, that may appear as a fold from the disc through zone I to zones II and III. The prognosis of this stage is poor.

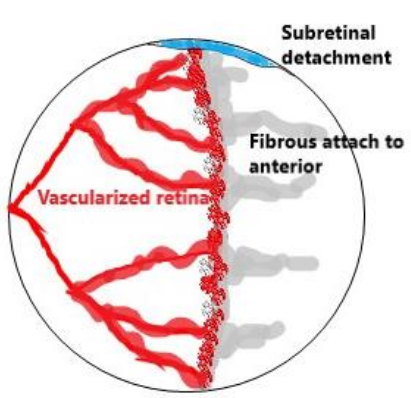

Figure 5 The picture shows extrafoveal partial retinal detachment.

- Stage 5 – Total retinal detachment: Retinal detachment is generally tractional and may be exudative. Characteristics are usually funnel-shaped and can be divides the funnel into an anterior and a posterior part; open - open, open – narrow, narrow – open, narrow – narrow. A first frequent configuration is open both

anteriorly and posteriorly, the retinal detachment has concave configuration and extends to the optic disc. A second frequent configuration is narrow in both its anterior and posterior aspects and the retinal detachment is located just behind the lens. A third, less common type, is the funnel that open anteriorly but narrowed posteriorly. The least common is the funnel that narrow anteriorly and open posteriorly.

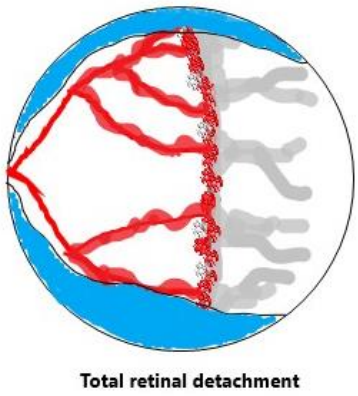

Figure 6 The picture shows total retinal detachment (open – open).

Plus disease is defined by a standard photograph and refers to marked arteriolar tortuosity and venous engorgement of the posterior pole vasculature at least 2 quadrants. It implies to the vascular shunting through the neovascularization. Plus disease refers to an active progression phase of disease and worse prognosis. The later it maybe increase the severity. It could found iris vascular engorgement, pupillary rigidity (poor pupillary dilatation) and vitreous haze.

Pre-plus disease is defined an intermediate “preplus” categorization in the revised international classification, 2005.

- An abnormal arteriolar tortuosity and venous dilation of the posterior pole which is insufficient for diagnosis of plus disease, but more arteriolar tortuosity and venous dilation than the normal retinal vessel. The vessels of preplus condition may progress to plus disease over time.

Aggressive posterior retinopathy of prematurity (AP-ROP) is an uncommon feature. The vascularization end in Zone I or very posterior Zone II and plus disease in all 4 quadrants, that out of proportion to the peripheral retinopathy. The disease is rapidly progressive and can progress to the retinal detachment without evolving through the typical stage 1 to 3 ROP. The Shunting vessel can occur from vessel to vessel within the retina and not be solely at the junction between vascular and avascular area. If this condition is untreated, it usually progresses to stage 5 ROP. Vitreous hemorrhage can occur in stage 3 to 5 . AP-ROP may appear only a flat network of neovascularization at the deceptively featureless junction between vascular and avascular area. This condition needs the close follow-up. The indirect ophthalmoscopy with a 20-D lens examination may help to distinguish the deceptively featureless neovascularization.

Regression of ROP: The most ROP is spontaneously regressing by the process of involution or evolution from vasoproliferative phase to fibrotic phase. The first signs of stabilization of the acute phase of ROP is the failure of progression of ROP to the next stage. The regression occurs at the junction of vascular and avascular area and the retinal vascularization advances to the periphery retina. The Involution of sequelae are the broad spectrum of peripheral, posterior retinal and vascular changes. The features during the process of involution are vascular abnormalities such as prominent areas of retinal avascularity, the abnormal branching of vessels with the formation of arcades, and telangiectasia. The pigmentary changes may be subtle, but it can be the large areas of hypo- or hyper-pigmentation. The pigmentary changes located along blood vessels and retinal pigment epithelium in avascular area. The circumferential retinovitreous interface changes can be a delicate line or more prominent ridges.

Table 2 The involutional Sequelae of Retinopathy of Prematurity.

Peripheral changes	Posterior changes
1. Vascular	
1.1 The Failure of peripheral retinal vascularization	1.1 Vascular tortuosity
1.2 Non-dichotomous branching of the retinal vessel	1.2 Straightening of the blood vessel in temporal arcade
1.3 The Vascular arcades with circumferential interconnection	1.3 Decreasing of the angle of insertion of major temporal arcade
1.4 Telangiectasia	
2. Retina	
2.1 Pigmentary changes	2.1 Pigmentary changes
2.2 Vitreoretinal interface change	2.2 Distortion and ectopia of the macula
2.3 Retina thinning	2.3 Straightening and folding of the retina in macular region leading to peripheral retina
2.4 Peripheral folds	2.4 Vitreoretinal interface change
2.5 Vitreous membrane with or without attachment to retina	2.5 Vitreous membrane
2.6 Lattice-like degeneration	2.6 Dragging of the retina over optic disc

Peripheral changes	Posterior changes
2.7 Retinal breaks	2.7 Tractional-rhegmatogenous retinal detachment
2.8 Tractional-rhegmatogenous retinal detachment	

2.2 WORLDWIDE ROP SCREENING FOR PRETERM INFANTS AND FOLLOW UP EXAMINATION

2.2.1 The American Academy of Pediatrics (AAP) and The American Academy of Ophthalmology (AAO) [27]

The guidelines for screening and treatment of this disease are different in each country. There are also different approaches of treatment in each hospital. The American Academy of Pediatrics (AAP) and The American Academy of Ophthalmology (AAO) recommend for screening in the infants with a birth weight of ≤1500 grams, gestational age (GA) of 30 weeks or less and Selected infants with a birth weight between 1500 and 2000 grams or gestational age of >30 weeks with an unstable clinical course such as requiring cardiorespiratory support or who are believed by their attending pediatrician or neonatologist to be at high risk for ROP. The retinal screening examinations performed after pupillary dilation and examination used binocular indirect ophthalmoscopy with a lid speculum and scleral depressor. The timing of first examination based on gestational age at birth as in the table 3, The timing developed from the evidence-based analysis of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) natural history data and confirmed by the Light Reduction in ROP Study (Light-ROP trial).

Table 3 The timing of first eye examination based on gestational age at birth (99% confidence for detecting Prethreshold ROP)

Gestational age at birth	Age for first eye examination	
	Postmenstrual	Chronological
22 weeks	31	9
23 weeks	31	8
24 weeks	31	7
25 weeks	31	6
26 weeks	31	5
27 weeks	31	4
28 weeks	32	4
29 weeks	33	4
30 weeks	34	4
Older than 30 weeks		4

The follow up examinations should be recommended on the basis of retinal findings classified according to the international classification as follows:

- 1 week or less follow up
    - Immature vascularization in zone I with no ROP
    - Immature retina extends into posterior zone II, near the boundary of zone I
    - Stage 1 or 2 ROP in zone I
    - Stage 3 ROP in zone II
    - The presence or suspected presence of aggressive posterior ROP
- 1 – 2 week follow up
    - Immature vascularization in posterior zone II
    - Stage 2 ROP in zone II

- Unequivocally regressing ROP: zone I

- 2 week follow up
  - Stage 1 ROP: zone II
  - Immature vascularization: zone II with no ROP
  - Unequivocally regressing ROP in zone II

- 2 – 3 week follow up
  - Stage 1 or 2 ROP in zone III
  - Regressing ROP: zone III

The retinal findings suggest that the examinations can be terminated as following:

- Zone III retinal vascularization attained without previous zone I or II ROP
- Full retinal vascularization end in close to 360° of the ora serrate. The mature retina found between the end of vascularization and the ora serrata. These criteria should be used for all infants who treated ROP with bevacizumab only.
- Postmenstrual age of 50 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present.
- Regression of ROP (the examiner make sure about there is no abnormal vascular tissue present because the disease can reactivate and progress in zone II or III).

2.2.2 Canadian Pediatric Society (CPS) clinical practice guidelines [28]

The recommendations for ROP screening were published as a Canadian Pediatric Society (CPS) clinical practice guideline in 2010 with the following: gestational age (GA) of $30\frac{6}{7}$ weeks or less (regardless of birth weight) or birth weights of 1250 grams or less as same as recommended by the United Kingdom or Guidelines for ROP screening but the individual centers in Canada may choose to

extend birth weight screening criteria to 1500 grams, as recommended by the AAP. In 2008 United Kingdom guideline development group found that 1 ROP infant was more than gestational age of 30 weeks and weighed more than 1250 grams by reviewed from 23 articles (10,481 preterm infants who were screened ROP). So the United Kingdom guideline recommended screening all infants with gestational age up to $30\frac{6}{7}$ weeks or with birth weights of less than 1251 grams. The Data from the Canadian Neonatal Network between 2003 and 2007 found that total 1,432 infants, who were more than gestational age of 30 weeks, had only 3 infants developed stage 3 ROP or greater and only 1 infant required treatment. The Screening of the infants with birth weights of between 1251 grams and 2000 grams is appropriated, if the neonatologist suggest that the infant to be at high risk because of the severity and the complexity of the neonatal clinical course. The risk factors were included the severe and unstable respiratory disease, hypotension requiring inotropes and prolonged ventilation or oxygen therapy. The timing of initial screening should performed at 31 weeks postmenstrual age (PMA) in the infant with gestational age $26\frac{6}{7}$ weeks or less and at 4 weeks chronological age (CA) in the infant with gestational age 27 weeks or more (as shown in the table 4).

Table 4 The initial screening for retinopathy of maturity

Gestational age at birth	Age for initial examination	
	Postmenstrual	Chronological
22 weeks	31	9
23 weeks	31	8
24 weeks	31	7
25 weeks	31	6
26 weeks	31	5
27 weeks	31	4

28 weeks	32	4
29 weeks	33	4
30 weeks	34	4
31 weeks	35	4
32 weeks	36	4

The duration of acute ROP screening depends on the ocular findings and PMA. CPS use the indications for stopping screening examinations, according to AAP as follows:

- Complete vascularization
- Zone III vascularization without previous zone I or II ROP
- PMA of 45 weeks and no prethreshold disease or worsening ROP
- Regression of ROP

2.2.3 The guidelines for ROP screening and treatment in Latin American Countries [5]

The guidelines for ROP screening and treatment in Latin American Countries, the following criteria are suggested 1. Birth weight: ≤ 1750 grams and/or gestational age ≤ 32 weeks 2. Birth weight > 1750 grams at the discretion of the neonatologist. That is the responsibility of the neonatologist to identify those infants who should be examined, determining the first examinations, and to notify the ophthalmologist for ROP screening examinations in a timely manner. The timing of the examination depend on the reliable estimated gestational age, at least 28 weeks should examine begin at 4-6 weeks after birth. These guidelines may need to be modified during the various gestational age as in the table 5.

Table 5 The timing of first eye examination based on gestational age at birth

Gestational age	Timing of first eye examination	Post gestational age
23 weeks	8	31 weeks
24 weeks	7	31 weeks
25 weeks	6	31 weeks
26 weeks	5	31 weeks
27 weeks	4	31 weeks
≥ 28 weeks	4-6 weeks	32 - 34 weeks

The follow up examinations of the guidelines:

- If the retina is immature and there is no ROP when examined, the next examination should be at next 2 - 3 weeks.
- If there is ROP in zone 3 when examination, the next examination should be at 2 weeks.
- If there is ROP zone 1 or 2 at the first examination, the next examination should be at 1 week, or at 3-4 days depending on the severity of disease by stage of ROP.
- The examinations should continue until the retina is fully vascularized (within 1 disc diameter of the ora serrata) or the ROP has regressed.

2.2.4 The guideline for screening of retinopathy of prematurity in South Africa [29]

The guideline for screening of ROP in South Africa are modified from the guidelines of the American Academy of Pediatrics and those of the United Kingdom. The recommendation of ROP screening in the all infants who born prior to 32 weeks gestation age or weighing <1500 grams or Preterm infants weighing 1500 - 2000 grams with may also be at risk of ROP such as a family history of ROP, cardiac

arrest, multiple (>2) blood transfusions, exchange transfusion or severe HIE. The ROP screening should be performed at 4 - 6 weeks chronological age or 31 – 33 weeks post-conceptional age, depend on whichever comes later. If the gestational age is uncertain, the chronological age should be used instead. The threshold ROP is usually reached by 37 weeks, therefore it is important to assess the infants before 37 weeks post-conceptional age. The follow up examination for ROP will be determined by the ophthalmologist.

The follow up examinations on the basis of retinal findings classified according to international classification as follows:

- 1 week or less follow up
    - Stage 1 or 2 ROP in zone I
    - Stage 3 ROP in zone II
- 1 - 2 weeks follow up
    - Immature vascularization in zone I (no ROP)
    - Stage 2 ROP in zone II
    - Regressing ROP in zone I
- 2 weeks follow up
    - Stage 1 ROP in zone II
    - Regressing ROP in zone II
- 2 - 3 weeks follow up
    - Immature vascularization in zone II (no ROP)
    - Stage 1 or 2 ROP in zone III
    - Regressing ROP in zone III

The presence of plus disease (defined as dilation and tortuosity of the posterior retinal blood vessels) in zones I or II suggests that the peripheral ablation is appropriate, rather than observation.

The examination findings suggest that the examinations can be terminated similar to The American Academy of Pediatrics (AAP) and The American Academy of Ophthalmology (AAO) recommendation include:

- Zone III retinal vascularization attained without previous zone I or II ROP
- Full retinal vascularization
- Postmenstrual age of 45 weeks and no pre threshold disease (stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present.
- Regression of ROP (care should be taken to ensure about no abnormal vascular tissue that is able to reactivation and progression).

2.2.5 UK Retinopathy of Prematurity Guidelines [30]

The evidence based practice guideline for the screening and treatment of ROP in UK was developed by the multidisciplinary guideline development group (GDG) of the Royal College of Pediatrics & Child Health (RCPCH) in collaboration with the Royal College of Ophthalmologists (RCOphth), British Association of Perinatal Medicine (BAPM) and the premature baby charity BLISS. The guideline was produced according to RCPCH standards for the guideline development. In this guideline provides 25 evidence based recommendations and 21 good practice points. The GDG recommendation base on the evidence base is remain the screening criteria in all infants with less than 32 weeks of gestational age (up to 31 weeks and 6 days) or birth weight less than 1501 grams. The sight-threatening ROP evidence is extremely unlikely to develop prior to 31 weeks postmenstrual age or 4 to 5 weeks postnatal age, that use for the setting of the first screening examination.

The timing of the first examination is given as postnatal rather than postmenstrual age as shown:

- Infants born before 27 weeks gestational age: the first screening examination should be examined in 30 - 31 weeks postmenstrual age.
- Infants born between 27 and 32 weeks gestational age: the first screening examination should be examined between 4 - 5 weeks (i.e. 28-35 days) postnatal age.
- Infants > 32 weeks gestational age, but with birth weight <1501 grams: the first ROP screening examination should be examined between 4 - 5 weeks postnatal age.
- Infants < 32 weeks gestational age or birth weight <1501 grams should have the first ROP screening examination prior to discharge.

The timing for the first screening for infants at risk of developing sight threatening ROP in related to the gestational age has been compiled as the table 6:

Table 6 The timing of first screen by gestational age

Gestational age at birth	Timing for first examination	
	Postmenstrual weeks	Postnatal weeks
22 weeks	30	8
23 weeks	30	7
24 weeks	30	6
25 weeks	30	5
26 weeks	30	4
27 weeks	31	4

Gestational age at birth	Timing for first examination	
	Postmenstrual weeks	Postnatal weeks
28 weeks	32	4
29 weeks	33	4
30 weeks	34	4
31 weeks	35	4

In the situations with no ROP and the vessels have only progressed to zone II or there is stage 1 or 2 disease without plus in zone II or III, the screening can be completed every 2 weeks.

The minimum frequencies of screening should be weekly when:

- The vessels end in zone I or posterior zone II
- There is any plus or pre plus disease
- There is any stage 3 disease in any zone

In all of the other conditions have been examined every 2 weeks until the criteria for termination have been reached.

The terminating screening examination in the infants who no ROP development, that is the minimal risk of developing sight-threatening ROP, is the vascularization has extended to zone III. In no ROP group, the examinations could be stopped after 36 weeks postmenstrual age.

The terminating screening examination in infants with ROP. The progressive active disease may be discontinued, when any of the following characteristics of regression are reaching at least 2 examinations, as follows:

- Lack of increase in severity
- Partial resolution progressing towards complete resolution
- Change in color in the ridge from salmon pink to white

- Transgression of vessels through the demarcation line
- Commencement of the process of replacement of active ROP lesions by scar tissue

2.2.6 The new guidelines for ROP screening in Sweden [31]

The Swedish guidelines for ROP screening are based on population-based studies and the guidelines have been modified continuously during the last 20 years. The study recommended for screening examination in all preterm infants who born before the gestational age of 33 weeks (Holmstrom et al., 1993). The guidelines for ROP screening were changed 10 years later, the screening recommended for preterm infants with gestational age less than 32 weeks (Larsson & Holmstrom, 2002). Nowadays, the new guidelines have screening criteria of gestational age < 31 weeks and start the first screening examination in the most immature infants at postmenstrual age of 31 weeks.

2.2.7 Screening for Retinopathy of prematurity in New Zealand [32]

The retinopathy of prematurity screening for the risk preterm infants has been practiced since the early 1980s in New Zealand. The first formal New Zealand ROP screening guidelines were established in 1990. The screening guidelines for ROP recommend in the all infants with birth weight less than 1250 grams or less than 31 weeks gestational age. There are a few tertiary neonatal intensive care units in New Zealand use screening examination by the gestational age of equal to or less than 30 weeks because there are low rates of severe ROP in among infants who born older than 30 weeks gestational age.

2.2.8 Retinopathy of prematurity screening criteria in Iran: new screening guidelines [33]

In the past 8.4% of Iranian ROP infants who required treatment would have been missed when applied the other countries screening recommendations in Iran. As a

results the revised of new screening guidelines in Iran have proposed the screening at gestational age ≤ 32 weeks or birth weight ≤ 2000 grams yielded 100 % sensitivity and 26.7 % specificity for ROP requiring treatment, that be regardless the clinical comorbidities. By the using screening recommendations of American Academy of Pediatrics would miss 25.4% of ROP and 8.4% ROP requiring the treatment.

2.2.9 The National Neonatology Forum of India (NNF) Clinical Practice Guidelines for Retinopathy of prematurity [6]

The gestational age of infants in India are not always known or accurately. There were reported ROP development in larger infants with a birth weight between 1500 and 2000 grams. There have been several reports ROP cases from ophthalmologists in the infants who had a birth weight between 1750 and 2000 grams. However, there is a paucity of population based data of ROP in the larger infants. There are concerns for screening all infants who had a birth weight of < 2000 grams, but that is unlikely to be feasible in the current situation because the limitation to access the ophthalmologists in India, so it's become the clinical practice guidelines for Retinopathy of prematurity in India.

The screening for ROP in India should be performed in all preterm infants who are born gestation ages < 34 weeks and/or birth weight < 1750 grams, or the preterm infants are born gestational age 34-36 $\frac{6}{7}$ weeks or birth weight 1750-2000 grams if they have risk factors for ROP. The risk factors for ROP in larger infants have not been clearly established. The first retinal examination should be examined no later than 4 weeks of chronological age or 30 days of life in infants who born gestational age ≥ 28 weeks. The infants born gestational age < 28 weeks or birth weight < 1200 grams should be early screening by 2-3 weeks of age for early identification of AP-ROP.

2.2.10 The clinical practices guidelines for Retinopathy of prematurity in Malaysia [34]

The guidelines was issued in 2005 and reviewed in 2007. The working group for the development of the guidelines consisted of the ophthalmologists from the Ministry of Health and Ministry of Education faculties of the government and the private sector. The guidelines are adapted from the guidelines on retinopathy of prematurity from the Royal College of Ophthalmologists and British Association of Perinatal Medicine.

The clinical practices guidelines screening for the preterm infants with either of the following:

- Birth weight less than 1500 grams
- Gestational age less than 32 weeks
- Infants with an unstable clinical course who are at high risk (as determined by the neonatalogist or paediatrician)

The first examination should be examined at 4 - 6 weeks after birth because examination in very early times may not have the benefit.

The screening of all infants at risk of ROP should be regularly examined until these conditions occurred:

- Retina is completely vascularization
- ROP fully regressed and there are no signs of risk for visual loss
- ROP has progressed to a level of severity where treatment is indicated

2.2.11 The recommended Philippines guideline for screening and referral of Retinopathy of prematurity (ROP) [35]

For the decades, the Philippines's criteria for screening set followed by the American Academy of Pediatrics, American Academy of Ophthalmology and the American Association for Pediatric Ophthalmology and Strabismus. However, the

recent evidence of ROP has occurred in the older and bigger infants, especially in the developing countries.

The recommended Philippines guideline for screening and referral of ROP had criteria for screening in all premature infants with < 35 weeks gestational age (GA) or birth weight (BW) < 2000 grams must be screened for ROP or Infants with GA ≥ 35 weeks or BW ≥ 2000 grams assessed by the attending pediatrician or neonatologist as having unstable clinical course should be screened for ROP. The presence of risk factors in premature infants should be alert the pediatrician/neonatologist to refer to ROP Screening:

- The perinatal risk factors: maternal infection during the 3rd trimester, placenta previa, poor nutrition, pre-eclampsia/eclampsia, premature rupture of membranes (PROM) ≥ 18 hours before delivery , multiple gestation
- The neonatal risk factors: oxygen supplementation (nasal cannula, mask, hood, CPAP or mechanical ventilation), anemia, interventricular hemorrhage, jaundice, respiratory distress syndrome, seizure, sepsis, blood transfusion[8].

The timing of screening

- The first examination must be performed at 2 weeks post-natal age (PNA) or at 32 weeks postconceptional age (PCA = GA + PNA), whichever comes earlier.
- If the infants referred for ROP screening cannot be examined due to the critical systemic condition, the examination should be rescheduled within 1 week of the intended examination.

2.2.12 The Royal College of Ophthalmologists of Thailand recommendations [13]

There are not the best of screening and treatment guidelines for ROP nowadays. Many researches study about the most effective methods of premature infant groups

and the timing for screening and treatments. In Thailand the Royal College of Ophthalmologists of Thailand recommendation, as following:

1. Infants with a birth weight of ≤ 1500 grams

2. Gestational age of 30 weeks or less

3. Selected infants with a birth weight between 1500 and 2000 grams or gestational age of >30 weeks with an unstable clinical course

An unstable clinical course can be classified into:

- Systemic illness
- Who are believed by their attending pediatrician or neonatologist to be at high risk for ROP

The timing of examination in the high risk ROP infants should examine begin at 4-6 weeks after birth or at 31 - 33 weeks postconceptional age, whichever comes later.

2.3 TREATMENT OF RETINOPATHY OF PREMATURITY (ROP)

The evolution of the treatment from the past to the present had been multimodalities for the treatment of ROP. First, the trans-scleral cryotherapy to the avascular retina was applied to treat ROP infants.

2.3.1 The multicenter trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)

The oldest main study is Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study that studied by Cryotherapy for Retinopathy of Prematurity Cooperative Group and published in Jan 29, 1988. A multicenter trial of cryotherapy for ROP was designed to evaluate its safety and efficacy. The study included 9,751 premature infants whom birth weight less than 1251 grams from 23 multi-centers. This study screened between 1 January 1986 to 30 November 1987, of which 291 infants with threshold ROP were randomized into 2 groups: 1. Peripheral retinal ablation with

cryotherapy group (the freezing of the external ocular surface, affecting sclera, choroid, and the full thickness of retina), that was performed within 72 hours 2. Observation (serve as the control group). In the control group, the infant with no ROP was observed or if existent ROP regressed before reaching the threshold, the infant was not eligible for cryotherapy in the trial. Informed consent was obtained from parent's premature infants prior to entry into the study and prior to randomization [36].

The threshold ROP was defined by contiguous 5 clock hours or cumulative non-contiguous 8 clock hours of stage 3 retinopathy of prematurity in zones 1 or 2 with plus disease. The plus disease was defined as a certain degree of dilatation and tortuosity of the retinal blood vessels in the posterior pole [36]. The threshold disease is a level of severity at which the risk of blindness was predicted 50%.

This study evaluated structure outcome and functional outcome in both groups. The structure outcome was documented with stereoscopic photographs of the posterior pole and anterior segment at 12 to 16 months after randomization. These stereoscopic photographs were submitted to the fundus photograph reading center with marked fashion. An unfavorable structural outcome was defined as 1. posterior retinal fold (usually involving the macula), 2. retinal detachment involving zone 1 of the posterior pole, or 3. retrolental tissue or "mass" obscuring the view of the posterior pole. The functional outcome was evaluated with monocular grating acuity assessments at 12 to 16 months after randomization. There were conducted by testers masked to the eye's randomization status, the ophthalmologist's subjective estimate of visual function, and the structural outcome. The visual acuity outcome was divided into 4 categories of functional response: 1. normal, greater than or equal to 1.6 cycles per degree, 2. below normal, 0.8 to less than 1.6 cycles per degree, 3. poor, less than 0.8 cycle per degree but measurable with one of the

standard acuity cards (not the low vision card), 4. blind or low vision. The functional outcome categories of visual acuity results were determined grouped into "favorable" and "unfavorable" group. The favorable group included the eyes in the normal and below normal categories. The unfavorable group included eyes in the poor and blind or low vision categories, which would be expected to have the poor long term prognosis of visual function.

The results of the study at preliminary 3 month outcome in the treated group of threshold ROP were superior to the untreated group. The overall treatment group can reduce unfavorable outcome about 50% compared with the control group (43% VS 21.8%) [3 6] . The results at 1 year were similar to 3 month found that the unfavorable outcome in 25.7% of the treated group of threshold ROP group compared with 47.4% of the control group (P<0.0001) [14]. The visual outcome at 1 year indicated that the unfavorable functional outcome in 35.0% of the treated group compared with 56.3% of the control group (P<0.0001). The visual acuity was 20/200 or worse in 44% of treated eyes and 62% of untreated eyes [14]. There was the benefit for visual function in the treated group. So these results of the study can conclude that the cryotherapy reduces the risk of unfavorable structural and functional outcomes from the threshold ROP. However, the treated infants frequently found the poor outcomes. About 21.8% progressed to macular dragging or retinal detachment with long term vision loss. The eyes with favorable anatomic outcomes of this study still had poor vision after long term follow up. About 31.9% of the treated eyes showed visual acuity results in the blind or low vision at 12 months after randomization.

Cryotherapy for Retinopathy of Prematurity Cooperative group (2001) evaluated the outcome at 10 years follow up after undergoing treatment with Cryotherapy compared with the control group of the study in Cryotherapy for Retinopathy of

Prematurity (CRYO-ROP) [37]. 10 years later, 247 children were examined both functional and structural outcome showed that fewer unfavorable outcomes in the treated with cryotherapy group than the controlled group: 44.4 % compared with 62.1% for distance visual acuity (P<0.001), 42.5 % compared with 61.6% for near visual acuity (P<0.001), and 27.2% compared with 47.9% for anatomical outcome (P<0.001). The total retinal detachment had been increased from 38.6% at follow up 5 years to 41.4% at follow up 10 years. In conclusion of the study found that the blinding of cryotherapy groups were less likely than the controlled group. The long term could preserve the visual acuity of near and distance vision in threshold ROP infants, who were treated by cryotherapy. The ROP infants who treated in the CRYO-ROP study were better outcomes than untreated ROP infants, but the structural outcome and visual outcomes were still unsatisfactory. Approximately 44% of treated infants were legally blind at 10 years and ROP in zone 1 almost always progressed to threshold ROP. The development of ROP treatment has been improved the rate of unfavorable outcome after the CRYO-ROP study, and then the benefits of earlier treatment of ROP infants were studied in the Early Treatment for Retinopathy of Prematurity (ETROP) study.

2.3.2 The Early Treatment for Retinopathy of Prematurity (ETROP) study [15]

In 2004, The ETROP study demonstrated the benefit of earlier treatment, particularly for the posterior disease. This study screened ROP at 26 participating centers between October 1999 to October 2002, of which 730 infants who birth weight less than 1251 grams were included in this study. In this study a researcher hoped of improving the rate of unfavorable outcome in the early treatment group. The timing indications for the treatment of ROP had been questioned: some investigators encouraged earlier treatment than CRYO-ROP study recommendation, but the others advocated conventionally timing of treatment. The study efforts to

identify treatment selection criteria, that expect only earlier treatment in the eyes at highest risk for developing threshold ROP and/or result in the unfavorable visual or structural outcome when absence of treatment.

The National Eye Institute funded a cooperative agreement to study the early treatment for Retinopathy of Prematurity (ETROP) study in 1999. There were 401 infants with a high risk (the prethreshold ROP type 1) were randomized into 2 groups: 1. The peripheral retinal ablation with laser therapy or cryotherapy (early treatment) group 2. The standard treatment (conventional management) group treats when develops the threshold ROP. There were 329 infants with low risk (the prethreshold ROP type 2) were observation (watch and wait approach). According to ETROP study should be considered for all cases of prethreshold type 1 ROP disease, defined as:

1. zone 1 ROP with plus disease
2. zone 1 stage 3 ROP without plus disease
3. zone 2 stage 2-3 with plus disease

And prethreshold type 2 ROP disease, defined as

1. Zone 1, stage 1 or 2 with no plus disease
2. Zone 2, stage 3 with no plus disease

Plus disease was defined as dilation and tortuosity of posterior pole retinal vessels in at least two quadrants, meeting or exceeding that of a standard photograph.

The final results of the study were measured the functional visual acuity, that assessed by the Teller acuity card procedure, and the structural examinations. The visual acuity outcome was divided into four categories of functional response: 1. normal was defined as greater than or equal to 3.70 cycles per degree, 2. below normal was defined as 1.85 to less than 3.70 cycles per degree, 3. poor was defined

as if less than 1.85 cycles per degree but measurable with one of the standard acuity cards (not the LV card), 4. blind/low vision (NLP, LP only, or LV only). These functional outcomes of grating acuity were divided into favorable and unfavorable outcome. The favorable group included the normal and below normal categories. The unfavorable group included the poor and blind/low vision categories, which was expected to have a poor long-term prognosis for visual function. The unfavorable structural outcome was defined as 1. a posterior retinal fold involving the macula, 2. a retinal detachment involving the macula, 3. retrolental tissue or mass obscuring the view of the posterior pole.

From the results of ETROP study, the clinical features of the ROP can classify the prethreshold ROP as high-risk or low-risk. In the high-risk prethreshold ROP that received the conventional management showed a much higher in progression to threshold disease than the low risk group (66.4% VS 15.5%) and a much higher in percentage of unfavorable structural outcome (10.0% VS 1.3%). The outcome after 9 month follow up demonstrated reduction in unfavorable visual acuity outcomes in the early treatment group from 19.5% to 14.5% (P=0.01), that was a significant benefit of treatment of the high-risk prethreshold ROP eyes and reduction in unfavorable structural outcomes (defined as retinal folds or detachment) in the early treatment group from 15.6% to 9.0% (P<0.001), that was a statistically significant benefit of treatment of eyes with high-risk prethreshold ROP.

The ETROP structural finding at age 2 years (The Early Treatment for Retinopathy of Prematurity Cooperative Group, 2006) found that the data were available for 339 of 374 (90.6%) of surviving children. The results shown that the unfavourable structural outcomes were reduced from 15.4% in conventionally managed group to 9.1% in early treatment group (P = 0.002) at 2 years of age [38]. The ophthalmic side effects (excluding retinal structure) from the ROP or its

treatment were not different between the both groups [38]. The outcome after 6-year of age follow up showed the visual benefit of early treatment group for infants of prethreshold type I ROP [39]. The result showed a benefit of visual acuity for prethreshold type 1 eyes in early treatment group compare with conventionally managed group (25.1% vs 32.8%, P=0.02), but not significant benefit of visual acuity for prethreshold type 2 eyes (23.6% vs 19.4%, P=0.37). Moreover, the early treatment group showed a significantly better structural outcome compared with conventionally managed group (8.9% vs 15.2% unfavorable outcome, $P < 0.001$). 52% of prethreshold Type II ROP showed the regression of ROP without the treatment [39]. So the results of the ETROP study confirmed the efficacy of treatment for the high-risk prethreshold ROP and redefined the indications for treatment.

2.3.3 The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP)

The peripheral retinal ablation with cryotherapy or conventional laser therapy were used in the past. That treatments were the destructive method and could not prevent the vision loss. In the Anti-vascular endothelial growth factor era, the vascular endothelial growth factor inhibitors drug was applied for ROP treatment, especially in the cases of ROP affecting in zone I. The use of anti-VEGF agents, primarily intravitreal Bevacizumab, is an emerging treatment for acute retinopathy of prematurity. In 2004, The Food and Drug Administration approved intravenous Bevacizumab therapy for the treatment of metastatic colon cancer. The mechanism has reduced the size and number of new vessels feeding of metastastasis. After that, the off-label of intravitreal Bevacizumab therapy for ophthalmological neovascular disorders began using.

The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP) [40] published in the New England Journal of

Medicine, 2011. This study is a prospective, multicenter randomized controlled trial to assess the benefit when used intravitreal Bevacizumab monotherapy for zone I or zone II posterior stage 3 with plus disease ROP. Infants were randomly assigned to receive intravitreal Bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. The study enrolled 150 infants (total sample of 300 eyes): 143 infants survived to 54 weeks' postmenstrual age. The results found that the recurred ROP for zone I and posterior zone II in 4 infants in the Bevacizumab group (6 of 140 eyes (4%)) and 19 infants in the conventional laser therapy group (32 of 146 eyes (22%), P=0.002). A significant treatment effect in zone I stage 3 with plus disease ROP (P=0.003) but not for zone II disease (P=0.27). The study found a lower rate of recurrent neovascularization for zone I ROP in the Bevacizumab treatment group when compared with the conventional laser therapy group. The revascularization found in the peripheral retinal vessel development. The vascularization was continued the vessel growth to avascular area after treatment with intravitreal Bevacizumab, but it had permanent destruction of the peripheral retina after treatment with conventional laser therapy.

CHAPTER 3

RESEARCH METHODOLOGY

The study design is Retrospective descriptive study and retrospective cohort study. The main purposes of the study are to evaluate the unfavorable outcomes and to assess the regression rate after early treatment protocol for the Retinopathy of Prematurity treatment in King Chulalongkorn Memorial Hospital.

3.1 TARGET POPULATION

The study included all premature infants who were screened Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital from January 2009 to January 2014.

3.2 SAMPLE SIZE

The researcher collects the data from all premature infants who were screened Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital from January 2009 to January 2014. First, the researcher collects the data from all premature infants who were screened and diagnosed as any ROP stage, any zone and with or without plus. We know the number of ROP infants, and then the no ROP infants were selected randomly with equal number of ROP infants.

3.2.1 Inclusion criteria

All eligible data from premature infants who were screened Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital from January 2009 to January 2014.

3.2.2 Exclusion criteria

The infants were lost follow up during the ROP follow up examination program before 45 weeks' postmenstrual age.

3.3 APPROACH TO PARTICIPANT

The data are retrieved from the medical records (IPD & OPD) of all infants who screened for ROP at ROP clinic, NICU and primaturity unit from January 2009 to January 2014 at the King Chulalongkorn Memorial Hospital.

3.4 RESEARCH INSTRUMENT

Instrumentation for the data collection use the case recording form for collecting the data from OPD cards and medical record form IPD charts, that can be divided into 4 parts, as following:

Parts 1 General data:

- Case in King Chulalongkorn Memorial Hospital or refer from other hospital
- Sex
- Twin A,B,C
- Gestational age (GA)
- Body weight (BW)
- Apgar score
- Systemic diseases

Parts 2 ANC data and peri-/post- natal complications:

- Maternal risks
- Perinatal complications and postnatal complications
    - intrauterine hypoxia, perinatal asphyxia, cyanosis, apnea, intraventricular hemorrhage, seizures, shock, acidosis, anemia, patent ductus arteriosus

Parts 3 ROP associated data:

- Screening time (GA/PCA)

- Oxygen therapy (type: box, mask, cpap, tube, timing, oxygen sat) and other therapy (blood exchange transfusion, blood transfusion)
- ROP staging, zone
- Plus disease
- The treatment and repeated of treatment (laser photocoagulation/ cryotherapy/Scleral buckling or a lens-sparing vitrectomy/ vitrectomy surgery combined with scissors dissection)
    - Parameters setting
- PCA at treatment
- Complication of treatment
    - Ocular: Eyelid and conjunctiva swelling, Corneal complication, VH, Endophthalmitis
    - Systemic: Bradycardia, Apnea
- Regression timing and regression rate in the treatment group
- Recurrence rate
- Progression

Part 4 Sequelae and complications:

- Sequelae and complications (follow up)
- Timing occur of sequelae and complications
- Unfavorable outcome: Retinal fold involving the macula, Retinal detachment involving the macula, Retrolental tissue or mass obscuring the view of the posterior pole, Macula and disc dragging

3.5 RESEARCH PROCESSING

3.5.1 Data collection process

First, the researcher will submit for institutional review boards (IRB) of Chulalongkorn University. Then, the researcher get the consent from IRB committee. We will make permission for collected the data of the study in King Chulalongkorn Memorial Hospital from the director of King Chulalongkorn Memorial Hospital. Finally, the researcher will collect the ROP data as planning.

3.5.2 Data analytical process

After the complete collect the data, the researcher will analyze the data by descriptive statistics in various aspects such as the demographics data analyze for frequency, percentage, the association risk factors for ROP development, the results of unfavorable outcomes after treatments, the incidence of regressed ROP, the progression of ROP and the recurrence of ROP after treatments and the amount of sequelae and complications after treatment.

3.6 DATA ANALYSIS AND STATISTICS

1. Demographic data of ROP and no ROP infants

- The data were analyzed by frequency and percentage.
- The comparison of gestational age and bodyweights between ROP and no ROP group were analyzed by independent t-test.

2. The association between maternal & infant risks and ROP developments

- A univariated analysis was performed using chi-square test and fisher's exact test to compare 2 independent groups for categorical variable.
- A multivariate analysis was analyzed all of the significant potential outcomes of univariated analysis between the risks and the ROP development ($p < 0.05$) by using forward binary logistic regression model for analysis.

3. Clinical unfavorable outcomes after treatments for ROP in King Chulalongkorn Memorial Hospital

- The data were analyzed by frequency, percentage and comparison between the early treatment protocol for ROP in KCMH group and the prethreshold type 1 group, using chi-square test and fisher's exact test to compare 2 independent groups.

4. Incidence of regressed ROP, progression of ROP and recurrence of ROP after treatments protocol in King Chulalongkorn Memorial Hospital

- The data were analyzed by frequency, percentage and comparison between the early treatment protocol for ROP in KCMH group and the prethreshold type 1 group, using chi-square test and fisher's exact test to compare 2 independent groups.

5. Sequelae and complications after treatment

- The data were analyzed by frequency, percentage and comparison between the early treatment protocol for ROP in KCMH group and the prethreshold type 1 group, using chi-square test and fisher's exact test to compare 2 independent groups.

3.7 ETHICAL CONSIDERATIONS

This research is clinical study in human. The researcher submitted for institutional review boards (IRB) of Chulalongkorn University. The Researchers are aware of the rights and respects of individuals. In the data collection process, there is no identified name or address of the preterm infants. The analysis results will only be used for academic purposes.

3.7.1 Respect for person

Data obtaining from the medical records (IPD & OPD cards) will be kept in privacy and employed only in this study. The data will be collected and assessed by

only principle investigator (Yothin Titawattanakul). The personal data will not be linkable to the study's result.

3.7.2 Beneficence/Non-maleficence

In this study is conducted in the retrospective fashion, so the participants will not get directly the benefit from this study. However, the results of this study can be further applied as guidelines for early treatment for Retinopathy of Prematurity treatment in the other hospitals.

3.7.3 Justice

All eligible data from premature infants who were diagnosed as any ROP stage in King Chulalongkorn Memorial Hospital from January 2009 to January 2014 will be recruited in the study.

3.8 RISK AND INVESTIGATOR'S RESPONSIBILITY

Risk to participants is low due to the retrospective design of the study.

CHAPTER 4

RESULTS

In this study is retrospective descriptive study and retrospective cohort study. The main objectives are to study unfavorable outcomes and assess the regression rate after early treatment protocol for the ROP in King Chulalongkorn Memorial Hospital (KCMH). The secondary objectives are to study the complications and sequelae after ROP treatment and evaluate progression and recurrence of ROP requiring retreatment after ROP treatment in KCMH. The sample of study is the infants with all gestational ages and birth weights, who had been screened for ROP at ROP clinic, Neonatal intensive care unit (NICU) and prematurity infants unit at KCMH since January 2009 to January 2014. All of ROP preterm infants, who were screened ROP during this period, have been included in the study. First, the study included any stage ROP, any zone and with or without plus disease of preterm infants among 96 preterm infants (183 eyes). Then, the no ROP cases among 96 preterm infants (192 eyes) were enrolled and randomly selected the equal number from infants, who were screened and not found ROP development at the same periods. The data were retrieved from the medical records (IPD & OPD) of all preterm infants and filled in the case recording form, that could be divided into 4 parts: (1) general data, (2) ANC data, perinatal and postnatal complications, (3) ROP associated data, (4) sequelae and outcome. The data in each part were used for answer the research question.

4.1 THE COMPARISON BETWEEN ROP GROUP AND NO ROP GROUP RESULTS

There were 375 eyes from 192 infants with all gestational ages and birth weights, who had been screened for ROP at ROP clinic, Neonatal intensive care unit (NICU)

and prematurity infants unit at the King Chulalongkorn Memorial Hospital since January 2009 to January 2014.

4.1.1 Demographics data of the infants

In this study were divided into Sex, Cases from KCMH or other hospital, Gestational ages, Bodyweights. A data were shown the data in table 7 for comparison between ROP group and no ROP group, as follows:

1. Sex, there were male 106 infants (54.2%) and female 86 infants (44.8%), classified into in ROP group were male 44.8% and female 55.2% and No ROP group were male 65.6% and female 34.4%

2. Cases from King Chulalongkorn Memorial Hospital or other hospital, the infants born in KCMH had 156 cases (81.3%) and 62 cases of this group founded the developing ROP, while the referral cases from other hospital had 36 cases (18.8%) and ROP in this group had 34 cases.

3. Gestational ages, the mean gestational ages of total infants of the study were 29.95 ± 2.75 weeks (range 23 – 40 weeks)

4. Bodyweights, the mean bodyweights in total infants of the study were bodyweights 1,356.44 ± 483.78 grams (range 535 – 3,290 grams)

When classified into the ROP group and no ROP group found that the mean gestational ages and body weights of ROP group were 28.48 ± 2.44 weeks (range 23 – 37 weeks) and 1,089.05 ± 340.82 grams (range 535 – 2,395 grams), respectively, while the no ROP group found that the mean gestational ages and body weights were 31.42 ± 2.22 weeks (range 27 – 40 weeks) and 1,623.83 ± 458.14 grams (range 860 – 3290 grams), respectively. Analysis of gestational age found that the preterm infants who developed any stage ROP and any plus disease were statistically significant born earlier than the infants who did not develop ROP, using independent t-test ($P<0.001$). The birth weights were

statistically significant lower in the preterm infants, who developed any stage ROP and any plus disease, compared to the infants who did not develop ROP, using independent t-test (P<0.001).

Table 7 The comparison of gender, gestational age, birth weight between ROP and No ROP group

Characteristics	ROP group	No ROP group	P value
Number of infants (No. of eyes)	96(183)	96(192)	
KCMH/Refer from other hospital n (%)	62 (64.58%)/ 34 (35.42%)	94 (97.92%)/ 2 (2.08%)	
Male/Female n (%)	43(44.79%)/ 53(55.21%)	63 (65.63%)/ 33 (34.37%)	
Gestational ages (weeks)	28.48 ± 2.44	31.42 ± 2.22	< 0.001 (independent t-test)
Birth weight (grams)	1,356.44 ± 483.78	1,623.83 ± 458.14	< 0.001 (independent t-test)

The comparison between KCMH case and Refer from other hospital

When analysis in ROP groups between KCMH cases and refer from other hospital cases found that the ROP treatment cases except the surgical cases (the stage 4 and 5 ROP) in KCMH had the early treatment protocol (the stage 3 ROP in any zone, any plus and could not be compatible with prethreshold type 1 ROP and threshold ROP) and prethreshold type 1 ROP among 40 eyes. In KCMH cases could be classified into the early treatment protocol had 32 eyes, while the prethreshold type 1 ROP had 8 eyes. When compare with the referral from the other hospital cases, the prethreshold type 1 ROP had 31 eyes and the early treatment protocol had 20 eyes. The data would seem to suggest that the most of KCMH cases were

early treatment before it turn to the prethreshold type 1 ROP, except in some cases when the ophthalmologist followed up and found prethreshold type 1 occurrence. In different from other hospital prefer the treatment when ROP progressed to the prethreshold type 1. Then, refer to KCMH for the ROP treatment (Table 8).

Table 8 The ROP staging between ROP cases in KCMH and refer from the other hospital

	KCMH cases	Other hospital cases	Total (No. of eyes)
Early treatment group, n (%)	32 (80.00%)	31 (60.78%)	63
Prethreshold type 1 group, n (%)	8 (20.00%)	20 (39.22%)	28
Total, No. of eyes (%)	40 (100%)	51 (100%)	91

4.1.2 The maternal risk and Retinopathy of Prematurity development

The maternal risks were collected the data from ANC records. According to the maternal risks found that the prolong PROM, IUGR, antepartum hemorrhage, maternal infection, TORCH infection, mild to severe preeclampsia, chronic hypertension superimposed preeclampsia, pregnancy induced HT, chorioamnionitis, placenta previa, polyhydraminos, anhydraminos and oligohydraminos, GDMA1 and GDMA2, HbE trait, elderly gravidarum, valvular heart disease and thyrotoxicosis were not statistically significant in univariate analysis for development ROP by using chi-square test or fisher's exact test ($P<0.05$) (Table 9).

Table 9 The association between maternal risk and ROP development

Maternal risk	ROP group n (%)	No ROP group n (%)	P value
PPROM			
- Yes	11/68 (16.18%)	17/96 (17.71%)	0.797†
- No	57/68 (83.82%)	79/96 (82.29%)	
IUGR			
- Yes	8/68 (11.76%)	4/96 (4.17%)	0.076‡
- No	60/68 (88.24%)	92/96 (95.83%)	
Mild to Severe preeclampsia	7/68 (10.29%)	15/96 (15.63%)	0.324†
- Yes	61/68 (89.71%)	81/96 (84.37%)	
- No			
Chronic HT superimposed	4/68 (5.88%)	1/96 (1.04%)	0.161‡
- Yes	64/68 (94.12%)	95/96 (98.96%)	
- No			
Chorioamnionitis			
- Yes	3/68 (4.41%)	2/96 (2.08%)	0.650‡
- No	65/68 (95.59%)	94/96 (97.92%)	
Placenta previa			
- Yes	3/68 (4.41%)	8/96 (8.33%)	0.365‡
- No	65/68 (95.59%)	88/96 (91.67%)	
GDM A1 and A2			
- Yes	7/68 (10.29%)	7/96 (7.29%)	0.498†
- No	61/68 (89.71%)	89/96 (92.71%)	
HbE trait			
- Yes	3/68 (4.41%)	6/96 (6.25%)	0.737†
- No	65/68 (95.59%)	90/96 (93.75%)	

Maternal risk	ROP group n (%)	No ROP group n (%)	P value
Elderlygravidarum			
- Yes	4/68 (5.88%)	4/96 (4.17%)	0.719‡
- No	64/68 (94.12%)	92/96 (95.83%)	
Anhydraminos and oligohydraminos			
- Yes	4/68 (5.88%)	4/96 (4.17%)	0.719‡
- No	64/68 (94.12%)	92/96 (95.83%)	
TORCH infection			
- Yes	2/68 (2.94%)	0/96 (0%)	0.170‡
- No	66/68 (97.06%)	96/96 (100%)	
Valvular HD			
- Yes	2/68 (2.94%)	0/96 (0%)	0.170‡
- No	66/68 (97.06%)	96/96 (100%)	
Thyrotoxicosis			
- Yes	2/68 (2.94%)	1/96 (1.04%)	0.570‡
- No	66/68 (97.06%)	95/96 (98.96%)	

- † Chi-square test
- ‡ Fisher exact test

4.1.3 The infant risk and Retinopathy of Prematurity development

The infant risks were collected from general data, perinatal and postnatal complications. A univariate analysis was performed by using chi-square test or fisher's exact test for analytical the results of infant risk factors impact on the ROP development. Infants, who developed ROP were statistically significant in lower Apgar score less than 7, when compared to the infants, who did not develop ROP ($P<0.05$). About twin and triplet infants were not statistically significant effect on ROP development. Severe RDS affected the infants, who developed any stage ROP and

any plus disease, which were statistically significant (P<0.05). On the other hand, mild and moderate RDS did not affect this condition. Birth asphyxia, shock, polycythemia, G6PD, anemia, jaundice, pneumothorax, hypoglycemia, UGIB and TTNB were not statistically significant for development of ROP (P<0.05). While IVH, Apnea, PDA, atelectasis, pneumonia were statistically significant effect on ROP development (P<0.05) (Table 10).

Table 10 The association between preterm infant risk factors and Retinopathy of Prematurity

Preterm infant risk	ROP group n (%)	No ROP group n (%)	P value
Twin			
- Yes	13/96 (13.54%)	23/96 (23.96%)	0.064†
- No	83/96 (86.46%)	73/96 (76.04%)	
Triplet			
- Yes	6/96 (6.25%)	4/96 (4.17%)	0.516†
- No	90/96 (93.75%)	92/96 (95.83%)	
Apgar			
- >7	53/69 (76.81%)	87/94 (92.55%)	0.004†
- ≤6	16/69 (23.19%)	7/94 (7.47%)	
Mild RDS			
- Yes	13/74 (17.58%)	16/96 (16.67%)	0.877†
- No	61/74 (82.43%)	80/96 (83.33%)	
Mod RDS			
- Yes	4/74 (5.41%)	9/96 (9.38%)	0.334†
- No	70/74 (94.59%)	87/96 (90.62%)	
Severe RDS			
- Yes	13/74 (17.57%)	3/96 (3.12%)	0.001†
- No	61/74 (82.43%)	93/96 (96.88%)	

Preterm infant risk	ROP group n (%)	No ROP group n (%)	P value
Birth asphyxia			
- Yes	9/74 (12.16%)	5/96 (5.21%)	0.102†
- No	65/74 (87.84%)	91/96 (94.79%)	
IVH			
- Yes	21/74 (28.38%)	6/96 (6.25%)	< 0.001†
- No	53/74 (71.62%)	90/96 (93.75%)	
Apnea			
- Yes	32/74 (43.24%)	21/96 (21.88%)	0.03†
- No	42/74 (56.76%)	75/96 (78.12%)	
Shock			
- Yes	4/74 (5.41%)	5/96 (5.21%)	1.000‡
- No	70/74 (94.59%)	91/96 (94.79%)	
G6PD			
- Yes	2/74 (2.70%)	7/96 (7.29%)	0.324†
- No	72/74 (97.30%)	89/96 (92.71%)	
Anemia			
- Yes	34/74 (45.96%)	18/96 (18.75%)	< 0.001†
- No	40/74 (54.05%)	78/96 (81.25%)	
PDA			
- Yes	42/75 (56.00%)	27/96 (28.12%)	< 0.001†
- No	33/75 (44.00%)	69/96 (71.88%)	
Congenital heart disease			
- Yes	4/74 (5.41%)	2/96 (2.08%)	0.405‡
- No	70/74 (94.59%)	94/96 (97.92%)	

Preterm infant risk	ROP group n (%)	No ROP group n (%)	P value
Jaundice			
- Yes	54/75 (72.00%)	80/96 (83.33%)	0.074†
- No	21/75 (28.00%)	16/96 (16.67%)	
Pneumothorax			
- Yes	4/74 (5.41%)	5/96 (5.21%)	1.000‡
- No	70/74 (94.59%)	91/96 (49.79%)	
Pneumonia			
- Yes	23/75 (30.67%)	13/96 (13.54%)	0.006†
- No	52/75 (69.33%)	83/96 (86.46%)	
Atelectasis			
- Yes	7/74 (9.46%)	2/96 (2.08%)	0.042‡
- No	67/74 (90.54%)	94/96 (97.92%)	
Hypoglycemia			
- Yes	14/74 (18.92%)	12/96 (12.50%)	0.249†
- No	60/74 (81.08%)	84/96 (87.50%)	
UGIB			
- Yes	7/74 (9.46%)	5/96 (5.21%)	0.283†
- No	67/74 (90.54%)	91/96 (94.79%)	
NEC			
- Yes	5/74 (6.76%)	2/96 (2.08%)	0.242†
- No	69/74 (93.24%)	94/96 (97.92%)	
TTNB			
- Yes	4/74 (5.40%)	10/96 (10.42%)	0.239†
- No	70/74 (95.60%)	86/96 (89.58%)	

- † Chi-square test
- ‡ Fisher exact test

4.1.4 Identified the significant associated risk factors for the development of Retinopathy of Prematurity

All of the significant potential outcomes of univariated analysis between the risks and the ROP development (P<0.05) were selected for multivariate analysis. Thereafter, using the forward binary logistic regression model for analysis. The significant associated risk factors were as follow: gestational ages (GA), bodyweights (BW), Apgar score less than 7, severe RDS, atelectasis, apnea, pneumonia, PDA, anemia and IVH. These risk factors were enrolled for multivariate analysis. In multivariate analysis of the associated risk factors found that bodyweights (BW), IVH and gestational ages (GA) were significantly associated with ROP development (P<0.05). The lower BW (BW 501-1,000 grams) (OR, 83.44; 95% CI, 3.31-2103.87; P=0.007) was the strong risk factor for ROP development, follow by lower GA (GA ≤ 27 weeks) (OR, 42.55; 95% CI, 2.73-659.99; P=0.007) and IVH (OR, 4.68; 95% CI, 1.35-16.19; P=0.015). Apgar score, severe RDS, atelectasis, apnea, pneumonia, PDA, anemia were included for multivariate analysis, but the results were not significantly associated with ROP development (Table 11).

Table 11 Forward stepwise binary logistic regression from the significant associated risk factors for the development of Retinopathy of Prematurity

Risk factors	OR	95% CI	P value
BW > 2,000 g	1.00		
BW 1,501 – 2,000 g	1.05	0.072-15.34	0.972
BW 1,001 – 1,500 g	2.01	0.14-28.14	0.605
BW 501 – 1,000 g	83.44	3.31-2103.87	0.007
GA ≥ 32 weeks	1.00		
GA > 30 - ≤ 32 weeks	1.52	0.22-10.41	0.672
GA > 27 - ≤ 30 weeks	3.44	0.55-21.55	0.187
GA ≤ 27 weeks	42.55	2.74-659.99	0.007
IVH	4.68	1.35-16.19	0.015

Risk factors	P value
Apgar score > 7	0.239
Apgar score 4-6	0.170
Apgar score <3	0.273
Severe RDS	0.800
Apnea	0.898
Anemia	0.680
PDA	0.616
Pneumonia	0.242
Atelectasis	0.804

4.2 THE COMPARISON BETWEEN THE EARLY TREATMENT PROTOCOL FOR THE ROP TREATMENT IN KCMH AND THE STANDARD TREATMENT (PRETHRESHOLD TYPE 1 AND THRESHOLD ROP) RESULTS

4.2.1 The Retinopathy of Prematurity classification groups of the study

All ROP infants of the study could be classified into 4 groups (Table 6) as follows:

1) Stage 1 and stage 2 ROP in any zone and no plus or pre-plus had 90 eyes (49.18%)

2) The early treatment protocol for the ROP treatment in KCMH (The early treatment protocol group) had 63 eyes (43.43%)

Nowadays, the standard treatment is the Prethreshold type 1 and Threshold ROP. While the early treatment protocol of this study is any stage 3 ROP in any zone and any plus and incompatibility with Prethreshold type 1 or threshold ROP. The early treatment protocol group of this study is as fellow:

1. ROP stage 3 zone 2 without plus 41 eyes and stage 3 zone 2 pre-plus 13 eyes (29.51%).

2. ROP stage 3 zone 3 without plus 6 eyes and ROP stage 3 zone 3 with pre-plus 3 eyes (4.92%).

In stage 3 zone 2 without plus or pre-plus ROP (Prethreshold type 2) were earlier treated than the previous standard practice of ROP treatment because the standard treatment of this group was observation and follow up. The treatment of ROP will be done, when it progress to the prethreshold type 1 or threshold ROP (the indication for standard treatment).

3) Prethreshold type 1 ROP had 28 eyes (15.30%)

From the data, in Prethreshold type 1 group of this study were all ROP stage 3 zone 2 with plus disease.

4) Stage 4 and stage 5 ROP had 2 eyes. There were stage 4, zone 2 with no plus on right eye and stage 5, zone 2 with no plus on left eye from 1 preterm infants (1.09%)

Table 12 ROP staging in ROP group of the study

ROP staging	Total no of eyes (%)
Stage 1 and 2 ROP	90 (49.18 %)
Early treatment protocol for the ROP treatment in KCMH	63 (29.51 %)
Prethreshold type 1 ROP	28 (15.30 %)
Stage 4 and 5 ROP	2 (1.09 %)
Total	183 (100 %)

4.2.2 The treatment modality for the Retinopathy of Prematurity in KCMH

The treatment in stage 1 and stage 2 in any zone and no plus or pre-plus ROP were observation (90 eyes). In the early treatment protocol group was treated with laser indirect ophthalmoscope (LIO) (63 eyes). The Prethreshold type 1 ROP was treated with laser indirect ophthalmoscope (26 eyes) and combined laser indirect

ophthalmoscope and intravitreal Bevacizumab (Avastin®) 0.0625 mg/0.025 ml (2 eyes). In stage 4 and stage 5 were encircling scleral buckling procedure and cryoretinopexy (2 eyes) (Table 13).

The post gestational ages at ROP treatment of this study were 37.13 ± 3.17 weeks (range 32 – 44 weeks), that could refer to the timing of neovascularization proliferation occur approximately 37.13 ± 3.17 weeks. This timing made the ophthalmologist to have the awareness of ROP progression.

Table 13 The treatment modality for Retinopathy of Prematurity staging in the study

ROP staging	Treatment modality				
	Observation	Laser LIO	Combined laser LIO and Intravitreal Bevacizumab	Surgery	Total no. of eyes
Stage 1 and 2 ROP	90	0	0	0	90
Early treatment protocol for the ROP treatment in KCMH	0	63	0	0	63
Prethreshold type 1 ROP	0	26 (92.86 %)	2 (7.14 %)	0	28 (100.00 %)
Stage 4 and 5 ROP	0	0	0	2	2

4.2.3 The regression rate after Retinopathy of Prematurity treatment in KCMH

Form the data of regression of ROP found that the ROP stage 1 and stage 2 in zone 2 or 3 with no plus or pre plus and no progression to stage 3 (throughout the follow examination until 54 weeks) among 90 eyes could be spontaneous regression without any treatment 100%. The early treatment protocol group could be divided

into 1. ROP stage 3 zone 3 without plus or pre plus who treated with laser LIO found that the regression rate after the treatment was 100 %. 2. Prethreshold type 2 ROP, who were stage 3 zone 2 without plus or pre-plus and treated with laser LIO found that the regression rate after the treatment was 100 % as well. The prethreshold type 1 ROP among 26 eyes were treated by laser LIO found that the regression rate was 88.46 % (23 eyes) and non-regression was 11.54 % (3 eyes). There were 2 eyes from 1 preterm infant, who was treated by combination between laser LIO and intravitreal Bevacizumab, found that the non-regression after treatment was 100%. ROP stage 4 and 5 could regress 50 % after surgery (Table 14).

Table 14 The regression after Retinopathy of Prematurity treatment in KCMH

ROP stage	Regression after the treatment		Total
	No	Yes	
Stage 1 and 2 ROP	0	90 (100%)	90
Early treatment protocol for the ROP treatment in KCMH	0	63 (100%)	9
Prethrehold type 1 ROP	5 (17.86%)	23 (82.14%)	28
Stage 4 and 5 ROP	1 (50.00%)	1 (50.00%)	2
Total	6 (3.31%)	175 (96.69%)	181

The regression compare between the early treatment protocol for the ROP treatment in KCMH group and the prethreshold type 1 group

ROP stage	Regression after the treatment		P-value
	No	Yes	
Early treatment protocol for the ROP treatment in KCMH	0	63 (100%)	0.002
Prethreshold type1 ROP	5 (17.86%)	23 (82.14%)	

As previously, the ROP treatment study (CRYO-ROP and ET-ROP) have been treated in the threshold ROP and the prethreshold type 1 ROP, but the early

treatment protocol for the ROP treatment in KCMH treated all of stage 3 ROP cases (including both ROP stage 3 zone 3 without plus or pre-plus and prethreshold type 2 ROP who were stage 3 zone 2 without plus or pre-plus) found that the early treatment protocol group had more the regression rate after treatment than the prethreshold type 1 ROP group, the difference between 2 groups was statistically significant by using fisher's exact test (P=0.002). When subgroup analysis of the early treatment protocol group, that was just only stage 3 zone 2 without plus or pre-plus disease group, found to be still more the regression rate after treatment than the prethreshold type 1 ROP group as well by using fisher's exact test (P=0.004).

The regression compare between early treatment (only stage 3 zone 2 without plus or pre-plus disease) and prethreshold type 1

ROP stage	Regression after the treatment		P-value
	No	Yes	
Early treatment protocol (only stage 3 zone 2 without plus or pre-plus disease)	0	54 (100%)	0.004
Prethreshold type 1 ROP	5 (17.86%)	23 (82.14%)	

4.2.4 The complication after Retinopathy of Prematurity treatment in KCMH

The most common complication after treatment with laser LIO is pre-retinal hemorrhage. It could be found in all groups and spontaneous recovery in all cases after follow up. In the early treatment protocol group found 8 eyes (13.60 %) after treatment that could be divided into ROP stage 3 zone 3 without plus or pre plus 4 eyes (6.80 %) and stage 3 zone 2 without plus or pre-plus 4 eyes (6.80 %) after treatment in each group. Vitreous hemorrhage in the early treatment protocol group found 2 eyes (3.40 %) that could be divided into ROP stage 3 zone 3 without plus or pre plus 1 eyes (1.70 %) and stage 3 zone 2 without plus or pre-plus 1 eyes (1.70 %). On the other hand, the prethreshold type 1 ROP group found pre-retinal hemorrhage among 4 eyes (14.81%) after treatment. There were not statistically

significant in differences between 2 groups by using chi-square test (P=0.628) (Table 15). Nowadays, the laser photocoagulation by LIO is a safe, effective and standard method for the treatment of ROP.

Table 15 The complications after Retinopathy of Prematurity treatment in KCMH

	Complications			P-value
	No	Preretinal hemorrhage	Vitreous hemorrhage	
Early treatment protocol for the ROP treatment in KCMH	9 (83.10%)	8 (13.60%)	2 (3.40%)	0.628
Prethreshold type 1 ROP	2 (84.60%)	4 (15.40%)	0 (0%)	

4.2.5 The average number of times of laser LIO treatment

In the early treatment protocol group had fewer frequency of laser LIO than the prethreshold type 1 ROP group. The number of times of laser LIO was 1.67 ± 0.696 times in early treatment protocol group compared with 2.18 ± 1.020 times in the prethreshold type 1 ROP group. There were no significant differences in statistical between 2 groups by using independent t-test (P=0.175).

4.2.6 The recurrence after Retinopathy of Prematurity treatment in KCMH

From the results of the study found that the recurrence of neovascularization after regression ROP and requiring re-treatment occurred in 2 eyes (7.14%) of the prethreshold type 1 ROP group, but no recurrence in the early treatment protocol group. There were not statistically significant in difference between 2 groups by using fisher's exact test (P=0.092). There were 2 eyes from 2 preterm infants in the prethreshold type 1 ROP group had regressed ROP after treatment before it progressed to ROP stage 4 (Table 16).

Table 16 The recurrence after Retinopathy of Prematurity treatment in KCMH

	Recurrence after the treatment		P-value
	No	Yes	
Early treatment protocol for the ROP treatment in KCMH	63 (100%)	0 (0%)	0.092
Prethreshold type 1 ROP	26 (92.86%)	2 (7.14%)	

4.2.7 The progression after Retinopathy of Prematurity treatment in KCMH

From the results of the study found that the progression after ROP treatment without regression ROP occurred in 3 eyes (10.71%) of the prethreshold type 1 ROP group, but no progression in the early treatment protocol group. There were statistically significant in difference between 2 groups by using fisher's exact test (P=0.027). There were 2 eyes from 1 preterm infants had been increasing the proliferation of neovascularization and created the traction to develop the retinal detachment (ROP stage 4 on the one eye and stage 5 on the other eye) after the treatment. This infant was treated with combined laser LIO and intravitreal Bevacizumab. There was 1 eye from 1 preterm infants had been increasing the proliferation of neovascularization and created the traction to develop the retinal detachment (ROP stage 5) after the treatment with laser LIO only (Table 17).

Table 17 The progression after Retinopathy of Prematurity treatment in KCMH

	Progression Regression after the treatment		P-value
	No	Yes	
Early treatment protocol for the ROP treatment in KCMH	63 (100%)	0 (0%)	0.027
Prethreshold type 1 ROP	25 (89.29%)	3 (10.71%)	

4.2.8 The unfavorable outcomes after Retinopathy of Prematurity treatment in KCMH

The unfavorable outcomes in ROP group founded 5 preterm infants (6 eyes in prethreshold type 1 cases and 2 eyes in ROP stage 4 and 5 case) as follows:

1. Preterm 31 weeks, BW 1,300 g, refer from other hospital had ROP stage 3 zone 2 with plus and treatment with LIO and Intravitreal Anti VEGF and repeat of laser LIO 2 times (2 eyes). In this case, the outcome had a total retinal detachment on 1 eye, the other eye had a tractional retinal detachment at nasal side, but some fibrovascular traction involving the macula.
2. Preterm 30 weeks, BW 1,300 g, case in KCMH had ROP stage 3 zone 2 with plus and treatment with LIO and repeat of laser LIO 2 times (1 eyes). When follow up until 57 weeks found the fibrovascular traction involving the macula.
3. Preterm 28 weeks, BW 1,460 g, refer form other hospital had ROP stage 3 zone 2 with plus on the both eye and treatment with LIO and repeat of treatment 2 times (2 eyes). The outcome found that the regressed ROP on the one eye, but the other eye progressed to retinal detachment (stage 4B) and refer to QSNICH. After the surgery still had the fibrovascular traction involving the macula.
4. Preterm 29 weeks, BW 1,370 g, refer form other hospital had ROP stage 3 zone 2 with plus on the both eye and treatment with LIO and repeat of treatment 3 times (2 eyes). The outcome found that ROP progressed to a tractional retinal detachment (ROP stage 5) on 1 eye. The other eye had ROP regression after treatment, then ROP had recurrence to develop ROP stage 4. This case refer to QSNICH (2 eyes). The final outcome had a total retinal detachment on 1 eye and had the fibrovascular traction involving the macula on the other eye.
5. Preterm 31 weeks, BW 1,800 g, refer form other hospital had ROP stage 4 and 5 in zone 2 with plus and treatment with surgery by scleral buckling procedure with a cryoretinopexy. The outcome after surgery had a tractional retinal detachment involve macula on 1 eye and could reattach of the retina after treatment on the other eye.

From the results of the study found that the unfavorable outcomes after ROP treatment in KCMH occur 6 eyes in the prethreshold type 1 ROP group but no unfavorable outcomes in the early treatment protocol group. There were statistically significant in difference between 2 groups by using fisher's exact test (P=0.001). The prethreshold type 1 ROP from other hospital had more the unfavourable outcomes after treatment than the case in KCMH because other hospital prefer the treatment when ROP progressed to the prethreshold type 1, that affected on the results after treatment.

Table 18 The unfavorable outcomes after Retinopathy of Prematurity treatment in KCMH

	Unfavorable outcomes		P-value
	No	Yes	
Early treatment protocol for the ROP treatment in KCMH	63 (100%)	0 (0%)	0.001
Prethreshold type 1 ROP	22 (78.57%)	6 (21.43%)	

CHAPTER 5

DISCUSSION, CONCLUSION AND SUGGESTIONS

5.1 DISCUSSION

Nowadays, there is no the best treatment of ROP for prevention the unfavorable outcomes after treatment. About the treatment study of the ROP since 1988, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study suggested the treatment for the threshold ROP. The result of the study found that the unfavorable outcomes in the treatment group was 21.8 %. Then, in 2003, the Multicenter Early Treatment for Retinopathy of Prematurity (ETROP) study considered treatment for the prethreshold type 1 ROP. The result of the study found that the unfavorable visual outcomes in the treatment group was 14.8 % and the unfavorable structural outcomes in the treatment group was 9.1 %. The result from the both standard treatments can imply that although the threshold ROP and the prethreshold type 1 ROP were received the treatment, the unfavorable outcomes still occurred with the treatment groups. The results of this study to compare the early treatment protocol for the ROP in King Chulalongkorn Memorial Hospital (KCMH) and the prethreshold type 1 ROP found that no unfavorable outcomes after the treatment in the early treatment protocol group, while the prethreshold type 1 ROP found 21.43 % of the unfavorable outcomes, similar to the outcomes from the previous study.

The result of the regression ROP after Retinopathy of Prematurity treatment in KCMH found that all of the early treatment protocol for ROP in KCMH group after treated with laser LIO had 100 % in regression rate, when compared with the prethreshold type 1 ROP group found that after treatment had 82.14 % in regression rate. All of the treated ROP infants who had non-regression in the prethreshold type 1 ROP group would turn to unfavorable outcomes at last.

The ocular and systemic complications in the ETROP study of treatment among the treated infant with the threshold ROP and prethreshold type 1 ROP found that the most common ocular complications were the conjunctiva and subconjunctiva hemorrhage 6.8 % in threshold ROP and 8.3 % in prethreshold type 1 ROP. The

hemorrhage (retinal, preretinal and vitreous) found 5.1 % in the threshold ROP and 3.9 % in the prethreshold type 1 ROP. The most common ocular complications of this study were preretinal hemorrhage found 15.4 % in the prethreshold type 1 ROP and 13.6 % in the early treatment group, followed by vitreous hemorrhage 3.4 % in the early treatment group. The most common systemic complications in the ETROP study were apnea, bradycardia or arrhythmia found 4.2 % in threshold ROP and 8.6 % in prethreshold type 1 ROP, but not found the systemic complications of the treatment for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital.

The data from the BEAT-ROP study showed that the intravitreal Bevacizumab was more effective than conventional laser therapy significantly for stage 3 ROP with plus in zone 1 but not zone 2. The rate of recurrence ROP with zone 1 disease was 42 % in laser group compared with 6 % in intravitreal Bevacizumab group (P=0.003), but with zone II posterior disease alone did was not differ significantly between the laser group and the Bevacizumab group (12 % in laser group and 5 % in intravitreous Bevacizumab group) (P=0.27). From the result of this study found that no recurrence after regressed ROP in the early treatment protocol for the ROP treatment in KCMH, when compare with the prethreshold type 1 ROP had 7.14 %, but the rate of recurrence ROP was not statistically significant between 2 groups.

The ETROP study found the progression of the prethreshold type 2 ROP about 22.1% to the prethreshold type 1 ROP. From the study found that if the prethreshold type 2 who had stage 3 in zone 2 with no plus or pre plus received the treatment by LIO, that had 100% no progression to the prethreshold type 1 ROP.

Most of the studies to determine the risk factors for ROP development had been carried out by using the univariate statistical methods, but it was not an appropriated method because the ROP was the multifactor disease. This study found out the association between the maternal, preterm infant risk factors and ROP development. First, to identify the significant risk factors by using univariated statistical methods. The gestational age (GA), body weights (BW), Apgar scores less than 7, severe RDS, IVH, apnea, anemia, atelectasis and pneumonia were statistically significant for

ROP development. Seconds, all of the significant potential risk factors were selected for multivariate analysis by using forward binary logistic regression model for analysis. The result found only the bodyweights (BW), IVH and gestational ages (GA) were statistically significant effect on ROP development, similar to many studies. Many studies found that the strongest risk factor for ROP development were bodyweights (BW) and gestational ages (GA). Some study found that IVH was associated the risk factor as well. However, other studies found the other of risk factor associated ROP development such as maternal diabetic, maternal preeclampsia, but in this study had no association.

5.2 CONCLUSION

The early treatment protocol for Retinopathy of Prematurity in King Chulalongkorn Memorial Hospital significantly reduced the unfavorable outcomes and increased the regression rate when compare with the previous standard early treatment of Retinopathy of Prematurity in the prethreshold type 1 ROP. Moreover, the early treatment protocol for Retinopathy of Prematurity in KCMH significantly reduced the recurrence and progression after treatment with the low complications.

5.3 THE STRENGTHS OF THIS STUDY

1. The ophthalmological examination and decision making for the treatment that are determined just only one ophthalmologist since January 2009 to January 2014.

2. There are a large number of the ROP eyes (183 eyes from 192 preterm infants) that enroll in this study. Moreover, there are varying stages of ROP and multimodality of treatments in KCMH.

5.4 THE LIMITATIONS OF THIS STUDY

This study is a retrospective descriptive study and retrospective cohort study. So the some collecting data from medical records are missing.

5.5 SUGGESTION

The prospective analytical study can clearly identify the structural and functional outcomes after ROP treatment and set up the timing for follow up examination of the

final outcomes. The prospective analytical study can complete the other significant data that associated with the outcomes after the treatment.

REFERENCES

1. Liu, L., et al., *Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals.* Lancet, 2016. **388**(10063): p. 3027-3035.
2. Lawn, J.E., et al., *Born too soon: accelerating actions for prevention and care of 15 million newborns born too soon.* Reprod Health, 2013. **10 Suppl 1**: p. S6.
3. Blencowe, H., et al., *Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010.* Pediatr Res, 2013. **74 Suppl 1**: p. 35-49.
4. Fierson, W.M., *Screening examination of premature infants for retinopathy of prematurity.* Pediatrics, 2013. **131**(1): p. 189-95.
5. Blindenmission, C., *Guidelines for ROP Screening and Treatment in Latin American Countries.* Brazil: Vision, 2007. **2020**.
6. Pejaver, R., A. Vinekar, and A.J.R.o.P. Bilagi, *National neonatology foundation's evidence based clinical practice guidelines 2010.* 2010: p. 253-262.
7. Jalali, S., et al., *Programme planning and screening strategy in retinopathy of prematurity.* Indian J Ophthalmol, 2003. **51**(1): p. 89-99.
8. กระทรวงสาธารณสุข, ส.ก., แนวทางตรวจคัดกรองและการดูแลรักษาโรคจอประสาทตาผิดปกติในทารกเกิดก่อนกำหนด. กรุงเทพมหานคร:กรมการแพทย์. 2547.
9. รักษ์, ข.ว.ก., *สภาวะ ตาบอด ตา เลือน ราง และ โรค ตา ที่ เป็น ปัญหา สาธารณสุข ใน เด็ก ไทย ปี พ. ศ. 2549-2550.* 2012.
10. (RNIB), R.N.I.o.B.P. *Retinopathy of Prematurity*. 2018, March; Available from: https://www.rnib.org.uk/eye-health/eye-conditions/retinopathy-of-prematurity.
11. Blencowe, H., et al., *National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications.* Lancet, 2012. **379**(9832): p. 2162-2172.
12. Network, T.C.N. *Canadian Neonatal Network Annual Reports*. Available from: https://www.canadianneonatalnetwork.org/portal/CNNHome/Publications.aspx.
13. ราชวิทยาลัยจักษุแพทย์แห่งประเทศไทย, แนวทางเวชปฏิบัติโรคทางจักษุวิทยาสำหรับจักษุแพทย์. 2548: โรงพิมพ์เรือนแก้วการพิมพ์.

14. Group, C.f.R.o.P.C., *Multicenter trial of cryotherapy for retinopathy of prematurity: one-year outcome: structure and function.* J Arch Ophthalmol, 1990. **108**: p. 1408-1416.
15. Good, W.V., *Early treatment for retinopathy of prematurity cooperative group Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial.* Trans Am Ophthalmol Soc, 2004. **102**: p. 233-248.
16. Christiansen, S.P., et al., *Progression of type 2 to type 1 retinopathy of prematurity in the Early Treatment for Retinopathy of Prematurity Study.* Archives of ophthalmology, 2010. **128**(4): p. 461-465.
17. Terry, T., *Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens*.* 1942.
18. Liu, P.-M., et al., *Risk factors of retinopathy of prematurity in premature infants weighing less than 1600 g.* J American journal of perinatology, 2005. **22**(02): p. 115-120.
19. Slidsborg, C., et al., *Neonatal risk factors for treatment-demanding retinopathy of prematurity: a Danish national study.* J Ophthalmology, 2016. **123**(4): p. 796-803.
20. Ryan, S.J., *Retina*. 4 th ed. 2006: Elsevier Inc.
21. Chan-Ling, T., B. Gock, and J. Stone, *The effect of oxygen on vasoformative cell division. Evidence that 'physiological hypoxia' is the stimulus for normal retinal vasculogenesis.* Invest Ophthalmol Vis Sci, 1995. **36**(7): p. 1201-14.
22. Kinsey, V.E., et al., *PaO2 levels and retrolental fibroplasia: a report of the cooperative study.* J Pediatrics, 1977. **60**(5): p. 655-668.
23. Khadawardi, E., F. Al Hazzani, and Vol, *Oxygen saturation and outcomes in preterm infants the BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups.* J Journal of Clinical Neonatology, 2013. **2**(2).
24. Flynn, J.T. and E. Bancalari, *On "Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes".* Journal of American Association for Pediatric Ophthalmology Strabismus

2000. **4**(2): p. 65-66.

25. Reynolds, J.D., et al., *Lack of efficacy of light reduction in preventing retinopathy of prematurity.* New England Journal of Medicine, 1998. **338**(22): p. 1572-1576.
26. Prematurity, I.C.f.t.C.o.R.o., *The international classification of retinopathy of prematurity revisited.* Archives of Ophthalmology, 2005. **123**(7): p. 991.
27. Ophthalmology, A.A.o.P.S.o., *Screening examination of premature infants for retinopathy of prematurity.* Pediatrics, 2013. **131**(1): p. 189-195.
28. Jefferies, A., *Retinopathy of prematurity: recommendations for screening.* Paediatrics child health, 2010. **15**(10): p. 667-670.
29. Visser, L., et al., *Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP).* SAMJ: South African Medical Journal, 2013. **103**(2): p. 116-125.
30. Wilkinson, A., et al., *UK retinopathy of prematurity guideline.* Eye, 2009. **23**(11): p. 2137.
31. Holmström, G., et al., *Evaluation of new guidelines for ROP screening in Sweden using SWEDROP–a national quality register.* Acta ophthalmologica, 2015. **93**(3): p. 265-268.
32. Dai, S. *Screening for Retinopathy of Prematurity in New Zealand*. 2014. 44-46.
33. Roohipoor, R., et al., *Retinopathy of prematurity screening criteria in Iran: new screening guidelines.* Archives of Disease in Childhood-Fetal Neonatal Edition, 2016. **101**(4): p. F288-F293.
34. Unit, H.T.A., M.D. Division, and M.o.H. Malaysia, *CLINICAL PRACTICE GUIDELINES RETINOPATHY OF PREMATURITY*. 2005.
35. (PAO), P.A.O.O., et al., *RECOMMENDED PHILIPPINE GUIDELINES FOR SCREENING AND REFERRAL OF RETINOPATHY OF PREMATURITY (ROP)*. 2013.
36. *Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group.* Arch Ophthalmol, 1988. **106**(4): p. 471-9.
37. *Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years.* Arch Ophthalmol, 2001. **119**(8): p.

1110-8.

38. Group, E.T.f.R.o.P.C., *The Early Treatment for Retinopathy of Prematurity Study: structural findings at age 2 years.* The British journal of ophthalmology, 2006. **90**(11): p. 1378.

39. Group, E.T.f.R.o.P.C., *Final visual acuity results in the early treatment for retinopathy of prematurity study.* Archives of ophthalmology, 2010. **128**(6): p. 663.

40. Mintz-Hittner, H.A., K.A. Kennedy, and A.Z. Chuang, *Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity.* New England Journal of Medicine, 2011. **364**(7): p. 603-615.

VITA

NAME	Yothin Titawattanakul
DATE OF BIRTH	12 March 1985
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	Bachelor of Medicine Program: BMA Medical College & Vajira Hospital, Mahidol University Diploma of the Thai Board of Ophthalmology: Faculty of medicine, Thammasat University
HOME ADDRESS	164 Soi Rama 2 38 Rama 2 road Bangmod Chomthong Bangkok 10150