Original Article/นิพนธ์ต้นฉบับ

Screening for Retinopathy of Prematurity in Queen Sirikit National Institute of Child Health: Bangkok, Thailand

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บทคัดย่อ

วัตถุประสงค์: เพื่อค้นหาอุบัติการณ์ของโรคเส้นเลือดจอประสาทตาผิดปกติในทารกแรกเกิดคลอดก่อนกำหนด (Retinopathy of Prematurity, ROP) ในเด็กทารกแรกเกิดที่ถูกส่งมารักษาตัวต่อยังคลินิก ROP สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

รูปแบบ: การศึกษาแบบย้อนหลัง

วิธีการศึกษา: เก็บรวบรวมข้อมูลจากเวชระเบียน ผู้ป่วยทารกแรกเกิดก่อนกำหนดที่ได้รับการตรวจและวินิจฉัย ROP จากคลินิก ROP ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างตุลาคม พ.ศ. 2549 ถึงกันยายน พ.ศ. 2552 โดยทารกทุกรายได้รับการตรวจจอประสาทตาหลังขยายม่านตาด้วย Indirect ophthalmoscope หลังอายุได้ 4 สัปดาห์ และติดตามอาการเป็นระยะจนกว่าเส้นเลือดจอประสาทตาจะสร้างเสร็จสมบูรณ์ โดยแบ่งกลุ่มผู้ป่วยตาม The International Classification for Retinopathy of Prematurity (ICROP) นำข้อมูลพื้นฐานผู้ป่วย, อาการแสดงทางคลินิก, โรคร่วม, การรักษาที่ได้รับ และผลการรักษามาวิเคราะห์

ผลการศึกษา: มีผู้ป่วยทารกแรกเกิด 655 รายจากทั้งหมด 1,609 ราย (ร้อยละ 40.7) ได้รับการวินิจฉัย ROP ระหว่างตุลาคม พ.ศ. 2549 ถึงกันยายน พ.ศ. 2552 อุบัติการณ์ของ ROP ไม่ลดลงตั้งแต่ พ.ศ. 2550 ทั้งนี้แบ่งเป็น pre-threshold and threshold ROP ร้อยละ 59 (n=387), Stage IV ร้อยละ 4 (n= 23), Stage V ร้อยละ 2 (n=14), and aggressive posterior ROP (AP-ROP) ร้อยละ 7 (n=47) มีผู้ป่วย 7 รายในกลุ่ม pre-threshold and threshold ROP ไม่ประสบความสำเร็จโดยการรักษาด้วยการยิงแสงเลเซอร์ที่จอประสาทตาและจำเป็นต้องได้รับการรักษาเพิ่มเติม ผู้ป่วยในกลุ่ม pre-threshold and threshold ROP จำนวน 27 ราย (ร้อยละ 7) ที่มีผลการรักษาไม่น่าพอใจเปรียบเทียบกับผู้ป่วย AP-ROP จำนวน 15 คน (ร้อยละ 31.9)

สรุป: อุบัติการณ์ของโรคเส้นเลือดจอประสาทตาผิดปกติในทารกแรกเกิดคลอดก่อนกำหนด (retinopathy of prematurity, ROP) ในคลินิค ROP ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ไม่ลดลงในช่วงเวลา 3 ปีของการศึกษาแม้ว่าจะมีการดูแลรักษาทารกแรกเกิดที่ดีขึ้น การตรวจสุขภาพตาร่วมกับการให้การรักษาอย่างรวดเร็วโดยเฉพาะในกลุ่ม high risk ROP เป็นสิ่งจำเป็นทั้งนี้การสำรวจข้อมูลทั่วประเทศไทยเป็นสิ่งจำเป็นเพื่อประเมินความแตกต่างของแต่ละภูมิภาคทั้งในแง่ความชุกของโรคและผลลัพธ์ **จักษุเวชสาร 2554; มกราคม-มิถุนายน 25(1): 9-16.**

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Original Article/นิพนธ์ต้นฉบับ

Screening for Retinopathy of Prematurity in Queen Sirikit National Institute of Child Health: Bangkok, Thailand

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Abstract

Objective: To determine the incidence of retinopathy of prematurity (ROP) in ROP clinic of Queen Sirikit National Institute of Child Health, Bangkok, Thailand

Design: Retrospective study

Methods: The medical records of preterm infants followed up in the ROP clinic between October 2006 - September 2009 were reviewed. All infants underwent dilated fundus examination by indirect ophthalmoscope after the fourth week of life and were followed up until the retinal vascularization was complete. Classification of ROP was done according to the International Classification for Retinopathy of Prematurity (ICROP). Detailed baseline characteristic, demographic information, co-morbidities, treatments and outcomes were collected and analysed.

Results: ROP was detected in 655 from 1,609 preterm infants (40.7%) screened in our ROP clinic during October 2006 - September 2009. The incidence of ROP cases did not declined since 2007. Among this group 59% (n=387) were classified as pre-threshold and threshold ROP, 4% (n= 23) as Stage VI, 2% (n=14) as stage V, and 7% (n=47) as aggressive posterior ROP (AP-ROP). Seven cases of pre-threshold and threshold ROP failed with laser photocoagulation and needed further treatment . There were unfavorable outcomes 27 cases (7.7%) in pre-threshold and threshold groups compared to 15 cases (36.6%) of AP-ROP.

Conclusions: The incidence of ROP in our ROP clinic did not decline despite improvements in overall care of the neonate during the 3 years of the study period . The need for ophthalmologic examination with early intervention for high risk ROP is important. A comprehensive countrywide survey of ROP in Thailand is needed to determine any regional differences in disease prevalence and outcomes. **Thai J Ophthalmol 2011; January-June 25(1): 9-16.**

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Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of blindness and impaired vision among premature neonates and is characterized by the proliferation of abnormal retinal blood vessels.[1] Attempts to clarify the etiology of ROP are still in progress, but low birth weight and low gestational age are well-known risk factors.[2-6] While the advancement of neonatal management has improved medical care and increased survival of premature infants, this seems to correlate with an increase risk for severe ROP and subsequent blindness.[7] As a result, the World Health Organization, in its program "VISION 2020-The Right to Sight," targeted all infants at risk for ROP for screening eye examinations and access to treatment for severe ROP.[8]

Various evidence-based screening criteria of ROP have been used for screening premature neonates.[9] The criteria have been determined in developed countries with high income, but it is not known whether these criteria would be suitable or applicable worldwide. The risk factors and screening criteria may show differences according to the progress in perinatal care, race, and country.[10,11] For this reason, it is advised to determine unit-specific criteria for ROP examination for each neonatal intensive care unit (NICU).[12]

Because the Queen Sirikit National Institute of Child Health is a tertiary center of child health in Thailand, the authors aimed to determine the incidence of ROP in the ROP clinic (referral : out-patient cases) of our institute.

Patients and Method

A hospital-based, retrospective study of premature infants with birth weight (BW) ≤1,500 grams and/or gestational age (GA) ≤ 28 weeks and/or unstable clinical course followed in ROP clinic between October 2006 - September 2009 were reviewed. The study and the data collection were compliant with the principles of the Declaration of Helsinki.

All infants underwent dilated fundus examination by indirect ophthalmoscope after the fourth week of life and were followed up until the retinal vascularization was complete. The pupils were dilated by application of mydriatic eye drops (2.5% phenylephrine and 1% tropicamide). The examination was performed using a lid speculum, depressor, binocular indirect ophthalmoscope, and 20- and 28-diopter lenses. Retinal findings were classified and staged according to the International Classification of ROP.[13,14] Examination was done weekly in cases of retinopathy, biweekly if progression was ascertained, and less frequent only if regression was evident. Need for treatment was based on the recommendations of the Early Treatment for Retinopathy of Prematurity Cooperative Group.[15] The infants who reached high-risk pre-threshold, threshold disease, and aggressive posterior retinopathy of prematurity (APROP) were classified as severe treatable ROP and treated with laser indirect ophthalmoscopy (LIO) or cryotherapy (Cryo) or combined with intravitreous bevacizumab (IVB). The infants with a more advanced stage of ROP were treated with retinal surgery. The anatomical outcome was assessed with a fundoscopic appearance in the last examination. Outcomes classified as unfavorable if the fundus revealed macular dragging, retinal detachment, or retrolental cicatrix formation. Detailed baseline characteristic, demographic information, co-morbidities, treatments and outcomes were collected.

Results

From a total of 1,609 infants examined, ROP was detected in 655 preterm infants (40.7%) screening in our ROP clinic during October 2006 - September 2009. The incidence of ROP cases did not declined since 2007 (Figure 1). ROP were found in 202 from

481 infants (42%) in the year 2007, 218 from 558 infants (39%) in 2008, and 235 from 570 infants (41%) in 2009. We found 86 cases of stage 1 ROP and 98 cases of stage 2 ROP without plus disease. We classified severe ROP to pre-threshold and threshold ROP 387cases (59%), stage IV 23 cases (4%), stage V 14 cases (2%), and aggressive posterior ROP (AP-ROP) 47cases (7%) (Figure 2).

Low GA and low BW were common factors (Tables 1 and table 2). Mean GA was 29.1 weeks (20-39 wk). Mean BW was 1,254.6 grams (545-2,670 g). Stage 3 ROP was the most common finding. Almost all severe ROP cases were treated with LIO (Figure 3). Fourteen cases of pre-threshold and threshold ROP failed with LIO and needed further treatment (13 cases combined with cryotherapy and 1 case combined with IVB, pars plana vitrectomy, and membrane peeling). LIO was done in all AP-ROP cases and combined with IVB in 2 cases. There were unfavorable outcomes 27 cases (7.7%) in pre-threshold and threshold group compare to 15 cases of AP-ROP (36.6%) (Table 3).

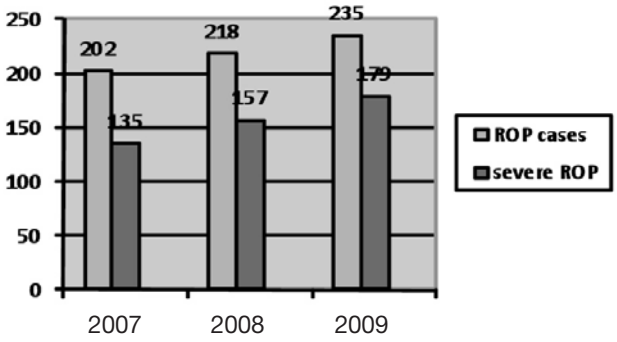

Figure 1. *Number of ROP (retinopathy of prematurity) cases during study period*

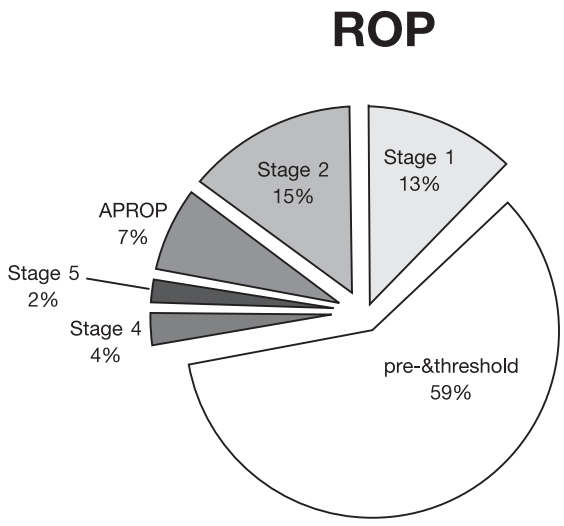

Figure 2. *ROP (retinopathy of prematurity) classification*

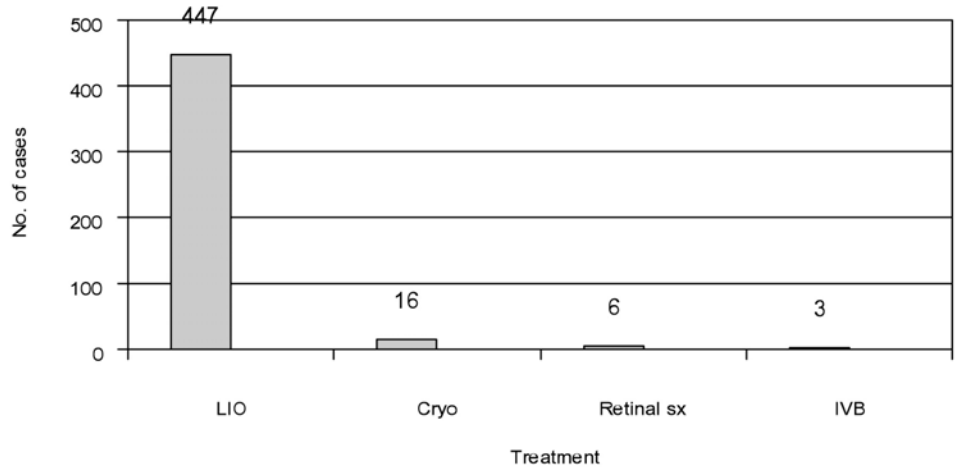

Figure 3. *Treatment for ROP*

Table 1 ROP in relation to gestational age

GA (weeks)	ROP (retinopathy of prematurity)							
	I	II	III	IV	V	APROP	Others*	Tot
• No data	5	5	2	3	3	2	0	20
• <28	14	32	88	10	1	7	1	153
• 28-30	36	79	159	10	8	15	1	308
• 31-32	17	25	51	0	1	15		109
• >32	12	19	25	0	1	8		65
Total	84	160	325	23	14	47	2	655

* = 1 cicatricial ROP, 1 regressed ROP

Table 2 ROP in relation to birth weight

Birth weight (grams)	ROP (retinopathy of prematurity)							
	I	II	III	IV	V	APROP	Others*	Tot
• No data	7	5	8	1	0	0	0	21
• <1,000	12	28	87	12	3	6	2	150
• 1,000-1,500	42	95	168	9	11	30	0	355
• 1,501-2,000	19	29	54	0	0	8	0	110
• >2,000	4	3	8	1	0	3	0	19
Total	84	180	325	23	14	47	2	655

* = 1 cicatricial ROP, 1 regressed ROP

Table 3 Outcome of Severe treatable ROP

Severe treatable ROP	Loss F/U	Favorable outcome	Unfavorable outcome
Prethreshold & Threshold ROP (N=387)	38 9.8%	322 (645 eyes) 92.3%	27 (53 eyes) 7.7%
AP-ROP (N=47)	6 12.8%	26 (52 eyes) 63.4%	15 (27 eyes) 36.6%
Total (N=434)	44 10.1%	348 (697 eyes) 89.2%	42 (80 eyes) 10.8%

Discussion

The etiology of ROP appears to be multifactorial. In addition to birth weight and gestational age, the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity reported multiple births, continuous oxygen therapy, and white race as risk factors for the development of ROP.[6] Although many studies have suggested various risk factors for ROP, there is substantial disagreement on the variables other than low birth weight and short gestational age.[16-20] Risk factors may show differences according to the improvements and variation in levels of neonatal care, socioeconomic factors, race, country, and various populations.[10,11] This hospital-based study represents the incidence and need for treatment for ROP in our institute as a tertiary center of a developing country with middle income and this current report cannot represent the true national incidence of ROP. Short gestational age and low birth weight, which were previously identified as risk factors for ROP,[3-5] were two risk factors in the current study. We found ROP in 153 infants (24.1%) with a GA of 28 weeks or less.

Most recently, the American Academy of Ophthalmology (AAO), the American Academy of Pediatrics (AAP), and the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) revised the previous statement for screening of premature neonates for ROP that was published in 2001.[21] Screening examinations are recommended for all neonates with a BW of less than 1,500 g or with an estimated GA of 32 weeks or less. Screening is also recommended for selected neonates with a BW between 1,500 and 2,000 g or a GA of greater than 32 weeks with an unstable clinical course, including those requiring cardio-respiratory support and who were judged to be at high risk. If we had not adapted these "and/or unstable clinical course" criteria[16] to screen all premature infants with BW $\leq$ 1,500 g and/or GA) $\leq$ 28 weeks, many infants with severe ROP would have been missed (19 cases with birth weight > 2,000 g with ROP and more than 174 cases with GA > 28 weeks with ROP).

The treatment rate for neonates with a birth weight of less than 1,000 g is 16.5% in our study compared to 6% in the CRYO-ROP study and 9% in the ET-ROP study.[22] There are various reports[23,24] describing the development of severe ROP in larger infants. Hutchinson et al[24] reported that previous

screening guidelines published by the AAP, AAPOS, and AAO may fail to detect severe ROP in larger, more mature infants. Our patient file of the infants with BW more than 2,000 g with severe ROP may have had multiple risk factors, but we could not collect all data because of a referral system defects.

In this study, 12 cases from 65 cases with GA more than 32 weeks and 4 cases from[19] cases with BW more than 2,000 g were stage 1 and showed regression spontaneously. 89.2% of severe treatable ROP cases had a favorable outcome with conventional treatment with LIO. The APROP group had more unfavorable outcome rates (36.6%) than the pre-threshold and threshold group (7.7%). This may be explained by different disease etiology and may need different clinical approach.[25-28]

This study has some limitations. Firstly, the study is retrospective. Secondly, our study population was referral out-patient cases. Incomplete chart retrieval, and loss of follow-ups were unavoidable. Finally, this study was from a single institution with a limited number of neonates and the data provided may not be representative of other medical centers in our country. Further comprehensive countrywide survey on ROP is needed to determine any regional differences in disease prevalence and outcomes. And this may be helpful for the determination of incidence, risk factors, and suitable screening criteria for ROP in Thailand.

References

1. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. Am J Ophthalmol 1942;24:203-4.
2. Kinsey VE, Arnold HJ, Kalina RE, Stern L, Stahlman M, Odell G, et al. PaO_2 levels and retrolental fibroplasia: a report of the cooperative study. Pediatrics 1977;60:655-68.
3. Ashton N, Ward B, Serpell G. Role of oxygen in the genesis of retrolental fibroplasia: a preliminary report. Br J Ophthalmol 1953;37:513-20.
4. Gunn TR, Easdown J, Outerbridge EW, Aranda JV. Risk factors in retrolental fibroplasia. Pediatrics 1980;65:1096-100.
5. Lucey JF, Dangman B. A reexamination of the role of oxygen in retrolental fibroplasia. Pediatrics 1984;73:82-96.
6. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology 1991;98:1628-40.
7. Giannantonio C, Papacci P, Molle F, Lepore D, Gallini F, Romagnoli C. An epidemiological analysis of retinopathy of prematurity over 10 years. J Pediatr Ophthalmol Strabismus 2008;45:162-7.
8. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020-the right to sight. Bull World Health Organ 2001;79:227-32.
9. Reynolds JD, Dobson V, Quinn GE, et al. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 2002;120:1470-6.
10. Lang DM, Blackledge J, Arnold RW. Is Pacific race a retinopathy of prematurity risk factor? Arch Pediatr Adolesc Med 2005;159:771-3.
11. Phan MH, Nguyen PN, Reynolds JD. Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle-income country. J Pediatr Ophthalmol Strabismus 2003;40: 208-12.
12. Gilbert C, Fielder A, Gordillo L, et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics 2005;115:e518-e525.
13. Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984;12:1130-4.
14. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. II. Arch Ophthalmol. 1987;105:906-912. Erratum in: Arch Ophthalmol 1987;105:1498.
15. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of Early Treatment for Retinopathy of

Prematurity Randomized Trial. Arch Ophthalmol 2003;121: 1684-94.

16. Schaffer DB, Palmer EA, Plotsky DF, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology 1993;100:230-7.
17. Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari HK. Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J India 1996;9:211-4.
18. Brown BA, Thach AB, Song JC, Marx JL, Kwun RC, Frambach DA. Retinopathy of prematurity: evaluation of risk factors. Int Ophthalmol 1998;22:279-83.
19. Becker H, Lieser K, Heler K. Effect and correlation of various risk factors in the development of retinopathy of prematurity: a retrospective study of 338 premature infants [article in German]. Klin Monatsbl Augenheilkd 1990;196:456-9.
20. Shah VA, Yeo CL, Ling YL, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore. Ann Acad Med Singapore 2005;34:169-78.
21. American Academy of Pediatrics, Section on Ophthalmology. Screening examinations of premature infants for retinopathy of prematurity. Pediatrics 2001;108:809-11.
22. Good WV, Hardy RJ, Dobson V, et al. The incidence and course of retinopathy of prematurity: findings from the Early Treatment for Retinopathy of Prematurity Study. Pediatrics 2005;116:15-23.
23. Jandeck C, Kellner U, Kossel H, Bartsch M, Versmold HT, Foerster MH. Retinopathy of prematurity in infants of birth weight > 2000 g after haemorrhagic shock at birth. Br J Ophthalmol 1996;80:728-31.
24. Hutchinson AK, O'Neil JW, Morgan EN, Cervenak MA, Saunders RA. Retinopathy of prematurity in infants with birth weights greater than 1250 grams. J AAPOS 2003;7:190-4.
25. Rajappa M, Saxena P, Kaur J. Ocular angiogenesis : mechanisms and recent advances in therapy. Adv Clin Chem 2010; 50:103-21.
26. Ells A, Guernsey DL, Wallace K, Zheng B, Vincer M, Allen A, Ingram A, DaSilva O, Siebert L, Sheidow T, Beis J, Robitaille JM. Severe retinopathy of prematurity associated with FZD4 mutations. Ophthalmic Genet 2010 Mar;31:37-43.
27. Mintz-Hittner HA, Best LM.Antivascular endothelial growth factor for retinopathy of prematurity. Curr Opin Pediatr 2009 Apr;21:182-7.
28. Law JC, Recchia FM, Morrison DG, Donahue SP, Estes RL. Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. J AAPOS 2010 Feb;14:6-10.