

Retinopathy of Prematurity in Infants with Late Retinal Examination

S. Zeinab Mousavi, MD; Reza Karkhaneh, MD; Mohammad Riazi-Esfahani, MD
Mohammad-Reza Mansouri, MD; Ramak Roohipoor, MD; Leila Ghalichi, MD
Malihe Kadivar, MD; Mehdi Nili-Ahmadabadi, MD; Fatemeh Naieri, MD

Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Purpose: To report the incidence, severity and risk factors of retinopathy of prematurity (ROP) in premature infants with late ROP examination in Farabi Eye Hospital.

Methods: In a retrospective study from January 2001 to July 2007, hospital records of premature infants who were examined later than 9 weeks after birth were reviewed to determine the incidence, severity and possible risk factors of ROP including gender, singleton or multiple gestations, gestational age (GA), birth weight (BW), oxygen therapy, blood transfusion, phototherapy, respiratory distress syndrome (RDS), mechanical ventilation, intraventricular hemorrhage and sepsis as well as age at initial examination.

Results: Out of a total of 797 infants referred for ROP screening during the study period, 216 (27.1%) had late examinations at a mean age of 141.7 ± 150.4 (range 64-1,460) days. Of these, 87 (40.3%) had different stages of ROP, 65 (30.1%) had stage 4 or 5 disease including 34 (16.2%) infants with stage 5 ROP in both eyes which was untreatable. Lower GA ($P < 0.001$), RDS ($P = 0.041$) and blood transfusion ($P = 0.009$) were associated with the development of ROP.

Conclusion: The overall prevalence of ROP and the incidence of severe ROP in particular, were unacceptably high in premature infants with late screening. These findings necessitate interventions to optimize timely referral for screening of premature infants.

Key words: Retinopathy of Prematurity; Risk Factors

J Ophthalmic Vis Res 2009; 4 (1): 24-28.

Correspondence to: Mohammad Riazi-Esfahani, MD. Associate Professor of Ophthalmology; Farabi Eye Hospital, Qazvin Sq., South Kargar St., Tehran, Iran, Postcode 13366-16351; Tel: +98 21 55418113, Fax: +98 21 55409095; e-mail: riazifahimi@yahoo.com

Received: July 6, 2008

Accepted: October 3, 2008

INTRODUCTION

Retinopathy of prematurity (ROP) is an uncommon but important cause of blindness¹ responsible for 50,000 annual cases of childhood blindness worldwide.² Considering the preventable nature of the condition, it is important to recognize and screen high risk newborns; this is of great concern in the VISION 2020 program, according to which all high risk infants should be examined six to seven weeks after birth.^{3,4} In 2006, the American Academy of Pediatrics, American Academy of Ophthalmology and

American Association for Pediatric Ophthalmology and Strabismus jointly announced that infants at risk for ROP must be examined at age 4-9 weeks based on gestational age (GA) such that an infant with GA of 22 weeks should be examined at 9 weeks after birth while infants above 26 weeks of GA should be examined at 4 weeks.⁵ It was previously recommended that these newborns should be examined at 7-9 weeks⁶ but there is uniformity in recommendations not to delay initial screening beyond 9 weeks of age.

Despite the emphasis on the importance

of timely screening for ROP, we still witness many high risk infants examined later than 9 weeks after birth with established complications of ROP, even blindness. This study was undertaken to determine the incidence, severity and risk factors for ROP in premature newborns with late retinal examination.

METHODS

In this retrospective study, we reviewed the hospital records of premature infants referred for ROP screening to the Pediatric Retina and Vitreous Division of Farabi Eye Hospital from January 2001 to July 2007. Clinical data included gender, singleton or multiple gestation, gestational age (GA), birth weight (BW), oxygen therapy, blood transfusion, phototherapy, respiratory distress syndrome (RDS), mechanical ventilation, intraventricular hemorrhage, sepsis and age at initial examination. All infants underwent indirect ophthalmoscopy using +20 and +30 D lenses after full dilatation of the pupils with tropicamide 0.5% and phenylephrine 1%. ROP was staged according to the international classification of ROP. Follow-up visits were scheduled based on the findings on the initial examination. Those patients who needed treatment were treated within 24 to 72 hours.^{7,8}

Severe ROP was defined as stages 3 or higher ROP requiring treatment or advanced untreatable disease. Criteria for treatment were based on the CRYO-ROP study until October 2003 as follows: threshold ROP including stage 3 in zone I or II that involves at least 5 consecutive clock-hour area or separate areas in 8 clock-hours.⁹ For patients treated thereafter, the ETROP study guidelines were employed: zone I any stage of ROP with plus disease or zone I stage 3 without plus disease, and zone II stage 2 or 3 ROP with plus disease.¹⁰ Stage 5 ROP with no apparent benefit from surgery was considered as advanced untreatable disease. Mild ROP was defined as ROP with no need for treatment.

The Chi-square test was used for analysis of dichotomous variables; for quantitative variables independent-samples *t*-test was employed with significance level set at $P < 0.05$. Logis-

tic regression analysis was performed to assess the compound effect of significant risk factors.

RESULTS

During the study period, 797 premature infants and neonates were examined for ROP, of whom 216 subjects (27.1%) underwent initial examination after 9 weeks of age (late screening). These included 120 (55.6%) male and 96 (44.4%) female patients. The infants had been born in hospitals inside the district of Tehran city in 74.1% and outside Tehran in 25.9% of cases. Mean age at initial visit was 141.7 ± 150.4 days (equivalent to 20.2 weeks) ranging from 64 to 1,460 days. Mean GA was 29.9 ± 2.7 (range 24-36) weeks and mean BW was $1,410 \pm 432$ (range 600-2,900) grams.

The overall prevalence of ROP was 40.3% in subjects with late examination and 29.2% in newborns screened before 9 weeks of age ($P = 0.004$). In the subset of patients with late screening, ROP was seen in 3 infants with GA > 32 weeks and BW > 1,500 grams. ROP was bilateral in 94.3% and included 2.8% mild ROP, 12.4% severe ROP requiring treatment and 25.1% advanced untreatable ROP.

Of 87 patients with late-screening ROP, 27 (31.0%) cases received treatment which included laser therapy in 16 (18.4%) patients, scleral buckling in 10 (11.5%) cases and vitrectomy in one (1.1%) subject. Stage 4 and 5 ROP were seen in 65 patients (30.1%), of whom only 10 (15.4%) cases underwent treatment including scleral buckling (7 patients), laser therapy (2 patients) and vitrectomy (one patient). These 65 subjects had mean GA of 28.1 ± 2.1 (range 24-35) weeks and mean BW of $1,244 \pm 365$ (range 650-2,450) gram. Stage 5 ROP was bilateral in 30 (13.9%) cases and no one was treatable.

In the late-examination subset, data on recommendations by pediatricians or neonatologists to parents for ROP screening were available in 119 cases. Of these, only 73 (61.3%) had been recommended to undergo screening before nine weeks of age. Of the remaining 46 (38.7%) subjects who were not examined earlier than 9 weeks of age, 13 (28.3%) patients were advised to seek screening after 9 weeks of age, 9 (19.6%) cases had been hospitalized for more

than 63 days but no retinal examination was performed meanwhile and no recommendation was offered in 24 (52.2%) cases. Of these 46 infants, 30 (65.2%) had ROP which was treatable only in 7 (15.2%) cases. Mean age at the time of initial retinal examination in these 46 infants was 88.0 days (12.6 weeks) greater than subjects who had been recommended to undergo timely screening ($P=0.001$). Moreover, mean age at initial examination in patients with severe ROP was 12.7 weeks greater than subjects without ROP ($P=0.001$). The prevalence of severe ROP was significantly higher in subjects who were recommended to undergo retinal examination after the age of 9 weeks (67.4%) as compared to those before that (27.8%, $P<0.001$).

Causes leading to obtaining an ophthalmologic evaluation in the 24 subjects who were not

offered any recommendation included noticing visual impairment in 8 (33.3%) cases, squint and abnormal eye movements each in one (4.2%) case, other eye disorders in 4 (16.7%) cases and recommendation by another physician during a routine visit in 4 (16.7%) subjects, but no data was available in the remaining 6 cases.

Table 1 summarizes potential risk factors for ROP based on univariate analysis, showing that GA and BW had significant effect on the occurrence of ROP. In patients with ROP mean GA was 2.5 (95% confidence interval [CI], 2.2-2.9) weeks lower and mean BW was 350 (95%CI, 288-412) grams lower as compared to subjects without ROP ($P<0.001$). Logistic regression analysis confirmed the role of GA, RDS and blood transfusion as significant risk factors for ROP (Table 2).

Table 1 Potential risk factors for retinopathy of prematurity based on univariate analysis

Risk factors	Odds ratio	95% confidence interval	P value
Gestational age	0.626	0.578-0.677	<0.001
Birth weight	0.998	0.998-0.998	<0.001
Gender	0.871	0.712-1.065	0.198
Multiple-gestation pregnancy	0.879	0.639-1.208	0.468
Oxygen therapy	0.237	0.092-0.611	<0.001
Blood transfusion	0.512	0.415-0.632	<0.001
Respiratory distress syndrome	0.603	0.417-0.870	0.005
Phototherapy	1.204	0.933-1.553	0.185
Mechanical ventilation	0.671	0.524-0.860	0.002
Intraventricular hemorrhage	0.757	0.550-1.042	0.126
Sepsis	0.813	0.458-1.445	0.509

Table 2 Independent risk factors of retinopathy of prematurity based on logistic regression analysis

	Odds ratio	95% confidence interval	P value
Gestational age	0.700	0.597-0.822	<0.001
Respiratory distress syndrome	0.527	0.286-0.973	0.041
Blood transfusion	0.441	0.237-0.818	0.009

DISCUSSION

ROP is a preventable cause of childhood blindness especially in countries experiencing third epidemics of the disease.¹¹ It seems that Iran is also experiencing the third epidemic of ROP and consequently is at high risk for ROP-related blindness.¹² ROP screening in high risk infants before 9 weeks of age and timely treatment of the condition decrease the rate of com-

plications and blindness.³⁻⁶ Current data on screening of premature infants and the incidence of ROP-related complications in Iran is scarce. The current study revealed that 27.1% of premature infants had late screening examinations. In a previous report covering data from 1999 to 2002 from our center, mean age at initial examination had been 25.1 weeks in patients with advanced ROP.¹² However, in a study from New Zealand in 1990 only one out of 85

premature infants (1.2%) was examined after 9 weeks (at 11 weeks) and had stage 4 ROP.¹³

An important finding of the current study was the high incidence of stage 4 and 5 ROP in infants with late examination (30.1%) which was treatable only in 15.4% (10 of 65 cases). We also encountered bilateral stage 5 disease in 13.9% of these patients which is equivalent to blindness. In contrast, there are studies not reporting a single case of stage 4 or 5 ROP.^{14,15}

In the current study, a proper recommendation was not offered to the parents for retinal examination of their premature baby in about 38.7% of subjects which is comparable to our previous report (48%, P=0.17),¹² indicating that the screening program did not show any improvement in the past few years.

The significant difference in both age at initial examination and stage of ROP between subjects who had been recommended to undergo examination before 9 weeks of age and those who had not, indicates the vital role of pediatricians and neonatologists in the timely diagnosis and management of ROP in order to decrease its burden of complications. Several studies have emphasized that a remarkable portion of ROP-related blindness is preventable in the presence of a structured screening program and by increasing awareness of ROP in physicians and parents.^{12,16-18} Another effective strategy for decreasing ROP-related blindness is performing retinal examinations in neonatal intensive care units (NICUs). A study showed that the rate of follow-up by parents is higher when their baby undergoes retinal examination during NICU admission.¹⁹

In line with previous studies, GA, BW,²⁰⁻²⁴ blood transfusion, mechanical ventilation,²² RDS,^{25,26} and oxygen therapy²⁶ were significant risk factors for ROP. Similarly, there was no significant correlation between ROP and gender,¹⁹ multiple births,²⁷ or phototherapy.²⁸

In this study we also encountered ROP among infants with higher range of GA and BW. Considering the fact that the range of GA and BW in ROP patients in developing countries are wider than those in developed countries,¹¹ we should revise the criteria for ROP screening and need population based studies to address this issue.

In summary, the overall prevalence of ROP and that of advanced disease seems to be significantly higher in infants with late retinal examinations. Recommendations for referral seem to be unacceptably inconsistent and inappropriate. These facts necessitate nationwide attempts to improve public awareness and coordinate the referral of premature infants for screening programs.

REFERENCES

1. Clemett R, Darlow B. Results of screening low-birth-weight infants for retinopathy of prematurity. *Curr Opin Ophthalmol* 1999;10:155-163.
2. Saugstad OD. Oxygen and retinopathy of prematurity. *J Perinatol* 2006;26(Suppl 1):S46-50; discussion S63-64.
3. O'Keefe M, Kirwan C. Screening for retinopathy of prematurity. *Early Hum Dev* 2008;84:89-94.
4. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020--the right to sight. *Bull World Health Organ* 2001;79:227-232.
5. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2006;117:572-576.
6. Palmer E A. Optimal timing of examination for acute retrolental fibroplasia. *Ophthalmology* 1981;88:662-668.
7. Section on Ophthalmology American Academy of Pediatrics. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2001;108:809-811.
8. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130-1134.
9. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. *Arch Ophthalmol* 1988;106:471-479.
10. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol* 2003;121:1684-1694.
11. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, 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:e518-525.

12. Karkhane R, Riazi Esfahani M, Lashay A, Chams H. A survey on visual impairment and blindness in children from retinopathy of prematurity. *Iranian J Ophthalmol* 2003;15:101-105.
13. Darlow BA, Clemett RS. Retinopathy of prematurity: screening and optimal use of the ophthalmologist's time. *Aust N Z J Ophthalmol* 1990;18:41-46.
14. Binkhathlan AA, Almahmoud LA, Saleh MJ, Srungeri S. Retinopathy of prematurity in Saudi Arabia: incidence, risk factors, and the applicability of current screening criteria. *Br J Ophthalmol* 2008;92:167-169.
15. Akkoyun I, Oto S, Yilmaz G, Gurakan, B, Tarcan A, Anuk D, et al. Risk factors in the development of mild and severe retinopathy of prematurity. *J AAPOS* 2006;10:449-453.
16. Modrzejewska M. Retinopathy of prematurity: clinical findings and current opinions on diagnosis and treatment. *Ann Acad Med Stetin* 2006;52:73-78; discussion: 78.
17. Azad R, Chandra P. Retinopathy of prematurity. *J Indian Med Assoc* 2005;103:370-372.
18. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev* 2008;84:77-82.
19. Attar MA, Gates MR, Iatrow AM, Lang SW, Bratton SL. Barriers to screening infants for retinopathy of prematurity after discharge or transfer from a neonatal intensive care unit. *J Perinatol* 2005;25:36-40.
20. Fortes Filho JB, Eckert GU, Procianoy L, Barros CK, Procianoy RS. Incidence and risk factors for retinopathy of prematurity in very low and in extremely low birth weight infants in a unit-based approach in southern Brazil. *Eye* 2007 Jul 6. [Epub ahead of print].
21. Hagadorn, JI, Richardson DK, Schmid CH, Cole CH. Cumulative illness severity and progression from moderate to severe retinopathy of prematurity. *J Perinatol* 2007;27:502-509.
22. Chen Y, Li XX, Yin H, Gilbert C, Liang JH, Jiang YR, et al. Risk factors for retinopathy of prematurity in six neonatal intensive care units in Beijing, China. *Br J Ophthalmol* 2008;92:326-330.
23. Montanez FJ, Olea JL. Eleven years experience in the management of retinopathy of prematurity in the Balearic Islands. *Arch Soc Esp Oftalmol* 2005;80:713-718.
24. McColm JR, Fleck BW. Retinopathy of prematurity: causation. *Semin Neonatol* 2001;6:453-460.
25. Karkhaneh R, Riazi Esfahani M, Ghojehzadeh L, Kadivar M, Nayeri F, Chams H, et al. Incidence and Risk Factors of Retinopathy of Prematurity. *Bina J Ophthalmol* 2005;11:81-90.[Article in Farsi]
26. Riazi Esfahani M, Karkhane R, Shokravi N. Assessment of retinopathy of prematurity among 150 premature neonates in Farabi Eye Hospital. *Acta Medica Iranica* 2001;39:35-38.
27. 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;34:169-178.
28. Seiberth V, Linderkamp O. Risk factors in retinopathy of prematurity. a multivariate statistical analysis. *Ophthalmologica* 2000;214:131-135.