

Risk Factors Evaluation of Threshold Retinopathy of Prematurity

Homeira Bigdeli, MD, MPH¹ • Ramak Roohipour, MD² • Reza Karkhaneh, MD³
Mohammad Riazi Esfahani, MD³ • Fatemeh Alipour, MD⁴ • Elham Ashrafi, PhD⁵
Nazanin Ebrahimi Adib, MD⁶ • Mohammad Zarei, MD⁴

Abstract

Purpose: This study aimed to evaluate risk factors associated with threshold retinopathy of prematurity (ROP) in premature infants referred to Farabi Eye Hospital during 2008-2009. Since blindness and severe visual impairments will occur in a high percentage of infants stricken with threshold retinopathy, we intended to examine relationship between demographic factors and threshold retinopathy in Farabi Eye Hospital, which, as a tertiary center, represents an appropriate sample of Iran's population.

Methods: In this retrospective case-control study, infants less than 37 weeks and/or birth weight less than 2,500 grams referred to Farabi Eye Hospital were included. The eyes were examined and a questionnaire was filled out for each infant. Based on the recording data, the relation between risk factors and threshold ROP was assessed.

Results: Out of 1,718 eyes participated in this study, 791 eyes had retinopathy. The incidence of threshold retinopathy in this study was 7.4 percent. We could figure out significant relationships between gestational age, birth weight, oxygen supplementation, duration of ventilation, blood transfusion, respiratory distress syndrome (RDS), postconceptual age and chronic respiratory disease with threshold ROP using independent sample *t*-test between two groups (infants with threshold retinopathy and infants without it). Cross-tab test revealed a significant relation between threshold retinopathy and risk factors such as sepsis ($p=0.006$), oxygen supplementation ($p=0.000$), blood transfusion ($p=0.004$), RDS ($p=0.000$), weight ($p=0.000$) age at first examination ($p=0.000$), and duration of ventilation. Logistic regression showed that the age (postmenstrual) more than 40 weeks at the time of first examination could be the predicting factors of threshold retinopathy.

Conclusion: The most important risk factors of threshold ROP are low gestational age, low birth weight, delayed in initial examination and the duration of oxygen therapy.

Keywords: Retinopathy of Prematurity, Threshold Retinopathy, Risk Factor

Iranian Journal of Ophthalmology 2014;26(1):48-52 © 2014 by the Iranian Society of Ophthalmology

1. General Practitioner, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Associate Professor of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
3. Professor of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
4. Assistant Professor of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
5. Epidemiologist, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran
6. Fellowship in Vitreoretina, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: February 26, 2014

Accepted: June 20, 2014

Correspondence to: Ramak Roohipour, MD

Associate Professor of Ophthalmology, Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, Email: ramakroohipour@yahoo.com

Introduction

Retinopathy of prematurity (ROP) is a main cause of childhood blindness, specially in infants with low birth weight and gestational age. The ROP outbreak does not follow a certain pattern in all countries, which could be caused by differences in gestational age, weight, ICU care and genetics.¹

Various strategies have been proposed in order to increase infants' survival and prevent morbidities. Preventions at the first and second levels include prevention of immature childbirth and prevention of other influencing risk factors respectively.²

More than 50,000 ROP-related blindness are reported throughout the world annually.^{3,4} Fortunately ROP resolves in at least 80 percent of cases without severe visual impairments.²

Nowadays the treatment approach for ROP is according to ETROP study but many patients which are referred to tertiary centers have developed threshold ROP which may lead to unfavorable outcome in at least 47 percent of patients, without treatment. Threshold retinopathy usually occurs at the 36th or 37th week of gestational age.⁵

About 50 percent of infants with untreated threshold retinopathy have severe visual impairments, while this figure is only five percent in the milder forms of ROP. Although the threshold ROP can be treated, it has high rate of unfavorable outcome.

In spite of great importance of threshold retinopathy, few studies have concentrated on retinopathy risk factors leading to threshold retinopathy.⁶

This study aimed at evaluating threshold retinopathy incidence and influence of demographic factors on it.

The main targets of retinopathy of prematurity screening are immediate diagnosis and prompt treatment.⁶

Since blindness and sever visual impairments will occur in a high percentage of infants stricken with threshold ROP, we would intend to examine relation between demographic factors and threshold ROP in Farabi Eye Hospital, as a tertiary center which represents an appropriate sample of Iran's population.

Methods

In this case-control study, the sample included all premature infants with gestational age less than 37 weeks and/or birth weight less than 2,500 grams which were referred to this hospital during 2008-2009. All infants had undergone ophthalmoscopy and fundus findings were recorded. The risk factors were recorded too. Based on the data, the relation between risk factors and threshold ROP was evaluated. The ROP positive eyes were included in the study then demographic data and risk factors were compared in non-threshold ROP, prethreshold ROP and ROP positive groups.

We used mean and standard deviation in case of quantitative variables and frequency percentage in case of qualitative variables. Additionally, we used Chi-square to analyze difference between two variables and Kolmogorov-Smirnov test and Mann-Whitney U test to analyze difference between quantitative and qualitative variables. Also, we applied logistic regression for categorizing and evaluation of predictive risk factors. All of variables with p-value under 0.2 after chi square analysis entered into Binary logistic regression. Recorded data were analyzed using SPSS version 15. The level of significance was set at 0.05%

Results

This descriptive study was carried out on 1,718 eyes of 859 infants with birth weight less than 2,500 grams and/or gestational age less than 37 weeks, referred to Farabi Eye hospital. Seven hundred ninty one eyes had ROP and 327 eyes needed treatment. The mean birth weight of screened patients was 1657.9 (± 565.52 SD) grams. The mean of gestational age was 31.6 (± 3.14 SD) weeks.

Threshold retinopathy in the ROP positive patients was observed in 59 eyes (7.4%).

The mean gestational age in infants with threshold ROP and non-threshold ROP were 29.8 ± 2.78 and 31.6 ± 3.14 weeks, respectively ($p \leq 0.001$). The mean birth weights in infants with threshold retinopathy and in non-threshold retinopathy were 1298 ± 498.32 and 1670.1 ± 563.9 grams respectively ($p = 0.001$). The duration of oxygen supplementation in infants with threshold retinopathy and non-threshold ROP group was 32.9 ± 20.1 and

16.7±17.6 days, respectively ($p=0.001$). Other demographic factors are displayed in (Table 1). The highest incidence of threshold ROP was in gestational age less than 26 weeks, which was significant ($p=0.007$). Also, the highest incidence of threshold retinopathy was in weight between 1000 to 1499 grams (37%). Sixty-six percent of threshold ROP eyes had birth weight less than 1,500 grams. The most frequent cause of reference was

pediatrician's advice, which was significant ($p=0.009$). In addition to above variables, sepsis, transfusion, RDS, reference manner, duration of ventilation, duration of oxygen supplementation were significant (Table 2). Logistic regression showed that sepsis and the age at first examination more than 40 weeks are the predicting factors of threshold retinopathy (Table 3).

Table 1. Univariate analysis of categorized and non-categorized factors associated with threshold ROP

Variable	Threshold ROP 59 eyes	Non-threshold ROP 732 eyes	p
Birth weight (gr)	1298.2±498.3	1670.1±563.9	0.001
Gestational age (wks)	29.8±2.78	31.6±3.14	0.000
postconceptual	83.5±21.6	103.2±102.5	0.001
Respiratory distress syndrome	49 (83%)	458 (62%)	0.000
Duration of artificial ventilation (days)	16.1±20.01	6.8±14.08	0.02
Duration of oxygen administration (days)	32.9±20.1	16.7±17.6	0.000
Chronic lung disease (no/yes)	40 (67%)	476(67%)	0.000
Transfusion (no/yes)	30(50.8%)	281(38%)	0.002
Phototherapy (no/yes)	45(76%)	545(74%)	0.1
Intraventricular hemorrhage (no/yes)	6(10%)	52(7.1%)	0.25
Sepsis (no/yes)	9(15%)	49(83%)	0.23

Notes: Values for non-categorized factors were expressed as means ±standard deviations
ROP: Retinopathy of prematurity

Table 2. Relation of demographic factors with threshold ROP (using χ^2 test)

Variable	Threshold ROP (eyes)	Non-threshold ROP (eyes)	p	odd ratio
Sex				
Male	30	408	0.4	0.9
female	29	445		
Age of first examination				
<30	23	408		
30-59	19	122	0.000	
60-89	10	46		
90-120	3	30		
>120	4	126		
GA<26wk	32	345	0.007	1.75
GA26-28wk	25	373		
Weight (gr)				
500-999	17	81		
1000-1499	22	335	0.000	
1500-1999	8	209		
>2000	12	107		
Oxygen duration (days)				
<7	8	198		
7-13	2	106	0.000	
14-21	8	122		
>21	40	306		
Ventilation duration (days)				
<7	34	496	0.000	
7-20	8	110		
>21	17	125		
Transfusion(yes/no)	30	281	0.004	
RDS(yes/no)	49	458	0.000	
IVH(yes/no)	6	52	0.26	2.43
Sepsis(yes/no)	9	49	0.006	
Phototherapy(yes/no)	45	545	0.1	
Refer from pediatrician	56	3	0.009	

Table 3. Logistic regression for determination of predicting factors

variable	B	p	EB (odd ratio)	95% confidence interval for eB	
	lower	lower	upper	Lower	upper
weight	0.683	0.241	1.980	0.632	6.208
oxygen	-0.786	0.278	0.456	0.11	1.883
ventilation	1.257	0.272	3.514	0.374	33.046
RDS	-0.585	0.259	0.557	0.202	1.537
Transfusion	-0.094	0.831	0.910	0.383	2.164
phototherapy	0.284	0.540	1.328	0.536	3.293
sepsis	-1.619	0.004	0.198	0.065	0.600
Age of first examination	-1.572	0.007	0.208	0.066	0.653

Discussion

In this study we examined the threshold ROP risk factors versus non-threshold patients (prethreshold and ROP positive). Threshold ROP incidence was demonstrated to be 7.4%. In this study, we found a significant relation between sepsis, oxygen supplementation, blood transfusion, RDS, weight, the age at first examination, and duration of ventilation with threshold ROP. Many of the previous studies didn't evaluate threshold retinopathy risk factors versus other groups of ROP.⁶ In the developing countries such as India and Saudi Arabia, the incidence of threshold retinopathy was higher than ours 45.1% and 26% respectively.^{7,8} But the incidence was lower in Belgium (6.4%) maybe because of the better cares offered in their infants unit.⁹ Yagi et al. reported higher incidence,¹⁰ while O'Conner et al reported a lower rate.¹¹ The incidence in this study was 7.4%.

In a study in India, transfusion was found as a significant factor in developing threshold ROP in infants with prematurity.⁷ Another study in Belgium found that developmental deficiency need to oxygen supplementation, and the mean airway pressure contribute in developing threshold ROP.⁹

In our study the highest incidence of threshold ROP was seen in subgroup with birth weight of 1000-1499 grams, but 33% of threshold ROP was registered in subgroup with birth weight more than 1,500 grams. In the study by Vinekar et al. highest incidence was in subgroup with higher weight and 26% of severe ROP had birth weight more than 1,250.⁷ In the report of Allegeret et al the highest rate of threshold ROP was reported in the subgroup with weight less than 750 grams.⁹ In our cases higher rate of threshold ROP which has been reported in more mature neonates may be due to less survival of our

neonates with low gestational age < 750 gr, so the screening criteria in developed country may not be applicable for our country.

Highest risk of developing threshold retinopathy in the present study was in gestational age of less than 26 weeks. But Allegeret⁹ and Manzoni¹² found highest risk in a lower gestational age. However, Dutta reported a similar finding as this study.⁶

The highest incidence of threshold retinopathy in the present study was among infants who received oxygen supplementation for 2-3 weeks, which was lower than findings of Dutta⁶ and Al-Essa.¹³

The incidence of chronic lung disease in our study among threshold patients was 30.6 percent, which was lower than the cases obtained by Allegert.¹⁴ In the present study, half of threshold retinopathy cases had received blood transfusion, which was a significant number. In the present study, 41.5 percent of threshold retinopathy cases had RDS, which was very significant. Lin reported similar findings regarding RDS.¹

Moreover, a low percentage of threshold retinopathy cases had intraventricular hemorrhage (IVH), which was not significant. In spite of high percentage of IVH in threshold retinopathy cases in Alessa and Lin^{1,13} their findings were not significant. In our investigation we found that the duration of oxygen therapy was a significant factor in developing threshold ROP. There are many controversies regarding oxygen therapy as a risk factor for ROP, but it seems that blood oxygen saturation is a more important factor in development of threshold ROP in cases with prethreshold retinopathy and oxygen saturation of >94% in room air is considered a higher risk factor.¹⁵

In our study, a significant relation was found between infants which had received oxygen supplementation for more than 21 days and threshold retinopathy, but this fact was not found significant in cases of O'Conner et al.¹⁰

Dutta found a high incidence of threshold retinopathy in infants who had received oxygen supplementation for more than 24 days, although it was not statistically significant. Allegaert et al reported a significant percentage of threshold retinopathy in their cases using oxygen supplementation for a longer period.^{6,9}

In the present study, although a high percentage of infants received phototherapy, there was no significant difference between infants who received phototherapy and those who did not receive it. Similarly, in Al-Essa et al reported while all threshold retinopathy cases had received phototherapy, there was no significant difference between threshold and non-threshold ROP groups.¹³

In our cases, there was no significant difference regarding sepsis between infants with threshold retinopathy and other ROP infants. Nevertheless, Al-Essa, Manzoni, and O'Conner found such risk factor significant.^{10,12,13} However, Allegaert didn't report a significant difference in his cases.⁹ In addition, Parupia et al reported a higher incidence of sepsis with a significant difference and a very high odds ratio in their report.¹⁶ Sepsis may injure developing blood vessels in the retina, inducing the release of cytokines or growth factors, inducing threshold ROP.^{11,17,18}

Conclusion

Threshold ROP was seen in patients with birth weight more than 1500 gram so screening criteria in developed countries may not be appropriate for us. The most important risk factors of threshold ROP are low gestational age, low birth weight, delay in initial examination of the neonates and the duration of oxygen therapy.

References

1. Lin HJ, Lin CC, Tsai SW, Lin HC, Su BH. Risk factors for retinopathy of prematurity in very low birth-weight infants. *J Chin Med Assoc* 2003;66(11):662-8.
2. Deb I, Bhowmik P, Ray D. Scenario of ROP in Rural Area of West Bengal. *AIOC* 2010; West Bengal, India.
3. Gergely K, Gerinec A. Retinopathy of prematurity—epidemics, incidence, prevalence, blindness. *Bratisl Lek Listy* 2010;111(9):514-7.
4. Bigdeli H, Roohipoor R, Karkhaneh R, Riazi Esfahani M, Shahim F, Ramezankhani A, et al. Structural outcome of treated retinopathy of prematurity patients. *Iranian Journal of Ophthalmology* 2012;24(1):56-65.
5. Carden SM, Luu LN, Nguyen TX, Huynh T, Good WV. Retinopathy of prematurity: postmenstrual age at threshold in a transitional economy is similar to that in developed countries. *Clin Experiment Ophthalmol* 2008;36(2):159-61.
6. Dutta S, Narang S, Narang A, Dogra M, Gupta A. Risk factors of threshold retinopathy of prematurity. *Indian pediatr* 2004;41(7):665-71.
7. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. *Indian J Ophthalmol* 2007;55(5):331-6.
8. Al-Amro SA, Al-Kharfi TM, Thabit AA, Al-Mofada SM. Retinopathy of prematurity at a University Hospital in Riyadh, Saudi Arabia. *Saudi Med J* 2003;24(7):720-4.
9. Allegaert K, Verdonck N, Vanhole C, de Halleux V, Naulaers G, Cossey V, et al. Incidence, perinatal risk factors, visual outcome and management of threshold retinopathy. *Bull Soc Belge Ophtalmol* 2003;(287):37-42.
10. Yagi M, Yamamori M, Morioka I, Yokoyama N, Honda S, Negi A, et al. VEGF 936C.T is predictive of threshold retinopathy of prematurity in Japanese infants with a 30-week gestational age or less. *Research and Reports in Neonatology* 2011;(1):5-11.
11. O'Connor MT, Vohr BR, Tucker R, Cashore W. Is retinopathy of prematurity increasing among infants less than 1250 g birth weight? *J Perinatol* 2003;23(8):673-8.
12. Manzoni P, Maestri A, Leonessa M, Mostert M, Farina D, Gomirato G. Fungal and bacterial sepsis and threshold ROP in preterm very low birth weight neonates. *J Perinatol* 2006;26(1):23-30.
13. Al-Essa M, Azad RV, Rashwan N. Threshold stage of retinopathy of prematurity: maternal and neonatal risk factors. *Ann Saudi Med* 2000;20(2):129-31.
14. Allegaert K, de Coen K, Devlieger H; EpiBel Study Group. Threshold retinopathy at threshold of viability: the EpiBel study. *Br J Ophthalmol* 2004;88(2):239-42.
15. McGregor ML, Bremer DL, Cole C, McClead RE, Phelps DL, Fellows RR, et al. Retinopathy of prematurity outcome in infants with prethreshold retinopathy of prematurity and oxygen saturation >94% in room air: the high oxygen percentage in retinopathy of prematurity study. *Pediatrics* 2002;110(3):540-4.
16. Haroon Parupia MF, Dhanireddy R. Association of postnatal dexamethasone use and fungal sepsis in the development of severe retinopathy of prematurity and progression to laser therapy in extremely low-birth-weight infants. *J Perinatol* 2001;21(4):242-7.
17. Liu PM, Fang PC, Huang CB, Kou HK, Chung MY, Yang YH, et al. Risk factors of retinopathy of prematurity in premature infants weighing less than 1600 g. *Am J Perinatol* 2005;22(2):115-20.
18. Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of prematurity—risk factors. *Indian J Pediatr* 2004;71(10):887-92.