Original Article

Retinopathy of Prematurity: Incidence, Risk Factors, and Outcome

Mohammad Kazem Sabzehei MD[1], Seyyed Abolfazl Afjeh MD•[2,3], Afsar Dastjani Farahani MD[3], Ahmad Reza Shamshiri MD[4], Fatemeh Esmaili BSc[3]

Abstract

Background: This study was planned to determine the rate, the predisposing factors, and the outcome of retinopathy of prematurity (ROP) in very low birth weight (VLBW) infants hospitalized in the neonatal intensive care unit (NICU) of a tertiary care hospital in Tehran.

Methods: All VLBW neonates admitted to the NICU, from April 2007 through March 2010 were enrolled. All relevant perinatal data, including the hospital course up to the time of discharge were documented. Repeated ophthalmologic examinations were done by a single ophthalmologist to observe the progression and subsequent resolution of ROP.

Results: Out of 414 infants undergoing ophthalmologic examination, ROP was detected in 71 infants (17.14 %); 3.4 % stage I, 8.7 % stage II, and 5.1 % stage III. ROP stages IV or V were not detected. After adjustment for different variables, the following independent risk factors were identified: VLBW (P = 0.002, OR = 4.89), multiple gestation (P = 0.001, R = 3.51), resuscitation at birth (P = 0.003, OR = 3), blood transfusion more than 45 mL/kg (P = 0.02, OR = 4.91), oxygen therapy for more than five days (P = 0.009, OR = 3.11), and age more than 10 days to regain birth weight (P = 0.008, OR = 1.06).Thirty-three patients with stages II and III ROP were treated with laser therapy, all of them improved and none progressed to blindness.

Conclusion: Our findings identify the major risk factors for ROP; skillful management of high-risk pregnancies, prevention of preterm births, appropriate neonatal care, high index of suspicion, routine screening, and prompt treatment are crucial to prevent the development and progression of ROP.

Keywords: Retinopathy of prematurity, risk factors, very low birth weight

Cite this article as: Sabzehei MK, Afjeh SA, Dastjani Farahani A, Shamshiri AR, Esmaili F. Retinopathy of prematurity: Incidence, risk factors, and outcome. *Arch Iran Med.* 2013; **16(9):** 507 – 512.

Introduction

Retrolental fibroplasia in premature newborns was first reported by Terry, et al. in 1942.[1] Subsequent studies identified oxygen therapy as the main cause of this complication and the condition was renamed as retinopathy of prematurity (ROP) by Heath in 1951.[2] Although various other factors have been recognized as predisposing triggers for the retinopathy during the last 60 years, still prematurity and low birth weight remain as the major risk factors for the occurrence of ROP.[3] This disease is the major cause of blindness in infants, and up to 70000 cases of blindness due to ROP have been reported up to date.[4] With the advent of new technologies and improved care for premature newborns, survival rates of extremely low birth weight (ELBW) neonates have jumped from 5 % to 65 % and those of very low birth weight (VLBW) infants from 35 % to 90 % during the recent years;[5] therefore, ROP is being increasingly diagnosed in these infants. Although, with proper care, most neonates develop mild degrees of ROP, but in some babies the condition is progressive and needs treatment.[6]

As early diagnosis and prompt treatment is crucial in preventing blindness,[7] this study was planned to determine the rate, the predisposing factors, and the outcome of ROP in VLBW infants hospitalized in the Neonatal Intensive Care Unit (NICU) of the Mahdieh Hospital and to compare our results with other centers in Iran and the world.

Authors' affiliations: [1]Hamedan University of Medical Sciences, Hamedan, Iran, [2]Pediatric Infections Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Mahdieh Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4]Dental Research Center, Dentistry Research Institute, Department of Community Oral Health, School of Dentistry, Tehran University of Medical Sciences, Tehran , Iran.

•Corresponding author and reprints: Seyyed Abolfazl Afjeh MD, Newborn Service, Mahdieh Medical Center, Shoosh Square, Shahrezad Street, Tehran, Iran. Tel: 98 21 55066282, E-mail: a_afjeh@sbmu.ac.ir, a.afjehi@gmail.com.

Accepted for publication: 10 July 2013

Methods

In this descriptive, cross-sectional study, all VLBW neonates admitted to the NICU in the Mahdieh Hospital in Tehran during the three years, from April 2007 through March 2010 were enrolled. Approval for the study was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences.

Neonates who died before a retinal examination were excluded from the study. All relevant perinatal data, including the hospital course up to the time of discharge, and the results of the eye examination were obtained from the case notes; follow ups at ophthalmologic clinic were documented.

Chronic lung disease (CLD) was diagnosed if the infant continued to need oxygen by the 36th week of gestation.[8] Intraventricular hemorrhage (IVH) was detected by intracranial ultrasonography and the severity was classified in accordance with Papile staging.[9] Necrotizing enterocolitis (NEC) was diagnosed on compatible clinical, laboratory, and radiologic manifestations according to the modified Bell criteria.[10]

Ophthalmologic examination was done by a single experienced ophthalmologist in accordance with the recommendations of the America Academy of Pediatrics (AAP),[11] using indirect ophthalmoscope with a 20 + lens and a speculum suitable for preterm noeonates. ROP was classified according to the international cri-

teria for ROP.[12] In accordance with the recommendations from the study "Early Treatment-Retinopathy of Prematurity (ET-ROP),[13] infants with the following stages of ROP were referred to the ophthalmology center: type 1 ROP (Zone 1, any stage with "plus" disease; Zone 2, stage 2 – 3 with "plus" disease; Zone 3, stage 3 with "plus" disease). Rest of the babies with type 2 ROP (Zone 1, stage 1 – 2 without "plus" disease; Zone 2, stage 2 – 3 without "plus" disease) were managed in our hospital and were followed up on discharge till complete vascularization of the retina and after checking for cyclo-refraction (the mean ophthalmologic examinations was three times), and the infants were divided into two groups according to the stage of ROP (Table 2). Categorical variables were reported as count and percentage and continuous variables as mean ± standard deviation (SD). To detect ROP risk factors, we performed simple and multiple logistic regressions with stepwise method, and odds ratio (OR) with 95 % confidence interval (95 % CI) were reported. P-values less than 0.05 considered as statistically significant. All data analyses were done with IBM SPSS Statistics for Windows (IBM Corp. Released 2011. Version 20. 0. Armonk, NY: IBM Corp).

Results

During the study period 564 VLBW newborns were hospitalized, of whom 414 neonates were followed up for development of ROP. The mean birth weight was 1268.57 ± 192.19 grams and the mean gestational age was 30.45 ± 2.29 weeks (79.71 % > 28 weeks, 20.29 % ≤ 28 weeks). Overall, 96.62 % of the neonates survived and were discharged from the hospital (Table 1).

Table1. Demographic and perinatal characteristics of the study neonates

Characteristic	No (N %)
Sex	
Female	206 (49.8 %)
Male	208 (50.2 %)
Birth weight (mean)	1268.57 ± 192.19
Birth weight(groups)	
1500–1251	247 (59.7 %)
1250–1001	114 (27.5 %)
≤ 1000	53 (12.8 %)
Gestational age	
> 28w	330 (79.7 %)
≤ 28w	84 (20.3 %)
Delivery type	
NVD	93 (22.5 %)
CS	321 (77.5 %)
Plurality	
Singleton	242 (58. 5 %)
Multiple	172 (41.5 %)
Maternal disease	
Yes	252 (60.9 %)
No	162 (39.1 %)
Antenatal steroid	
Yes	414 (100 %)
No	0 (0 %)
Apgar /1'	
≥ 6	321 (77.5 %)
< 6	93 (22.5 %)
Apgar/ 5'	
≥ 6	394 (95.2 %)
< 6	20 (4.8 %)
Resuscitation at birth	
Yes	136 (32.8 %)
No	278 (67.2 %)
RDS	
Yes	266 (64.3 %)
No	148 (35.7 %)
Chronic lung disease	
Yes	97 (23.4 %)
No	317 (76.6 %)
Pneumothorax	
Yes	24 (5.8 %)
No	390 (94.2 %)
Pulmonary hemorrhage	
Yes	21 (5.1 %)
No	393 (94.9 %)
Surfactant	
Yes	243 (58.7 %)
No	171 (41.3 %)
Apnea	
Yes	164 (39.6 %)
No	250 (60.4 %)
Sepsis	
Yes	10 (2.4 %)
No	404 (97.6 %)
IVH > grade2	
Yes	15 (3.6 %)
No	399 (96.4 %)
PDA	
Yes	140 (33.8 %)
No	274 (66.2 %)
NEC > stage2	
Yes	3 (0.7 %)
No	411 (99.3 %)
Dopamine	
Yes	12 (2.9 %)
No	402 (97.1 %)
Blood transfusion(mL/kg)	
None	185 (44.7 %)
< 45	113 (27.3 %)
> 45	116 (28.0 %)
Duration of mechanical ventilation	
None or <5 days	402 (97.1 %)
≥ 5 days	12 (2.9 %)
Duration of oxygen therapy	
≤ 5 days	237 (57.3 %)
> 5 days	177 (42.7 %)
Age of regaining birth weight (day)	16.47 ± 9.5
ROP ≥ stage2	
Yes	57 (13.8 %)
No	357 (86.2 %)
Hospital course (day)	38.2 ± 21.73
Outcome	
Survived	400 (96.6 %)
Expired	14 (3.4 %)

On unilateral analysis, risk factors identified for development of ROP were: gestational age ≤ 28 weeks, birth weight < 1250 grams, resuscitation at birth, respiratory distress syndrome (RDS), nasal continuous positive airway pressure (CPAP), surfactant therapy, mechanical ventilation for > five days, CLD, pulmonary hemorrhage, patent ductus arteriosus (PDA), pneumothorax, hypotension needing inotrope therapy, age to regain birth weight,

Table 2. Simple regression analysis results for ROP

Characteristic	ROP stage < 2 (n = 357)	ROP stage ≥ 2 (n = 57)	OR	95%CI	P-value
Sex					0.7
Female	179 (86.9 %)	27 (13.1 %)	1		
Male	178 (85.6 %)	30 (14.4 %)	1.12	1.96–0.64	
Birth weight (g)					
1251–1500	232 (93.9 %)	15 (6.1 %)	1		
1001–1250	92 (80.7 %)	22 (19.3 %)	3.7	7.44–1.84	< 0.001
≤ 1000	33 (62.3 %)	20 (37.7 %)	9.37	20.09–4.37	< 0.001
Gestational age					< 0.001
> 28w	300 (90.9 %)	30 (9.1 %)	1		
≤ 28w	57 (67.9 %)	27 (32.1 %)	4.74	8.56–2.62	
Multiple gestation					0.13
Yes	143 (83.1 %)	29 (16.9 %)	1.55	2.72–0.88	
No	214 (88.4 %)	28 (11.6 %)	1		
Maternal disease					0.84
Yes	218 (86.5 %)	34 (13.5 %)	0.94	1.67–0.53	
No	139 (85.8 %)	23 (14.2 %)	1		
Apgar score /1´					0.08
≥ 6	282 (87.8 %)	39 (12.2 %)	1		
< 6	75 (80.6 %)	18 (19.4 %)	1.74	3.21–0.94	
Apgar score/ 5'					0.008
≥ 6	344 (87.3 %)	50 (12.7 %)	1		
< 6	13 (65 %)	7 (35 %)	3.7	9.73–1.41	
Resuscitation at birth					< 0.001
Yes	100 (73.5 %)	36 (26.5 %)	4.41	7.91–2.45	
No	257 (92.5 %)	21 (7.5 %)	1		
RDS					< 0.001
Yes	211 (79.3 %)	55 (20.7 %)	19.03	79.24–4.57	
No	146 (98.6 %)	2(1.4 %)	1		
CLD					< 0.001
Yes	56 (57.7 %)	41 (42.3 %)	13.77	26.23–7.23	
No	301 (94. 9 %)	16 (5.1 %)	1		
PDA					< 0.001
Yes	103 (73.6 %)	37 (26.4 %)	4.56	8.23–2.53	
No	254 (92.7 %)	20 (7.3 %)	1		
Pneumothorax					0.007
Yes	16 (66.7 %)	8 (33.3 %)	3.48	8.56–1.41	
No	341 (87.4 %)	49 (12.6 %)	1		
Pulmonary hemorrhage					0.05
Yes	15 (71.4 %)	6 (28.6 %)	2.68	7.23–1	
No	342 (87 %)	51 (13 %)	1		
Surfactant therapy					< 0.001
Yes	195 (80.3 %)	48 (19.7 %)	4.43	9.3–2.11	
No	162 (94.7 %)	9 (5.3 %)	1		
Apnea					0.001
Yes	130 (79.3 %)	34 (20.7 %)	2.58	4.57–1.46	
No	227 (90.8 %)	23 (9.2 %)	1		
Sepsis					0.45
Yes	10 (100 %)	0 (0 %)	2.27	0.36– infinity	
No	347 (85.9 %)	57 (14.1 %)	1		
IVH (grade > 2)					0.48
Yes	12 (94.7 %)	3 (5.3 %)	0.63	2.29–0.17	
No	345 (96.6 %)	54 (3.4 %)	1		
NEC (stage > 2)					0.35
Yes	2 (66.7 %)	1 (33.3 %)	3.17	35.54–0.28	
No	355 (86.4 %)	56 (13.6 %)	1		
Hypotension requiring inotrope (dopamine)					0.001
Yes	6 (50 %)	6 (50 %)	6.88	22.15–2.14	
No	351 (87.3 %)	51 (12.7 %)	1		
Blood transfusion (mL/kg)					
None	181 (97.8 %)	4 (2.2 %)	1		
< 45	106 (93.8 %)	7 (6.2 %)	2.99	10.45–0.85	0.09
> 45	70 (60.3 %)	46 (39.7 %)	29.74	85.68–10.32	< 0.001
Duration of mechanical ventilation					0.06
None or < 5 days	349 (86.8 %)	53 (13.2 %)	1		
≥ 5 days	8 (66.7 %)	4 (33.3 %)	3.29	11.32–0.96	
Duration of oxygen therapy					< 0.001
≤ 5 days	226 (95.4 %)	11 (4.6 %)	1		
> 5 days	131 (74 %)	46 (26 %)	7.21	14.41–3.61	
Age Of Regain Birth Weight (D)	15.15 ± 7.8	24.77 ± 13.97	1.11	1.15–1.07	< 0.001

Table 3. Multiple regression analysis with adjusted estimates of odds ratio (95% CI)

Characteristic	OR	95 % CI	P-value
Birth weight (g)			
1500–1251	1		
1250–1001	1.8	4.23–0.77	0.23
≤ 1000	4.89	13.31–1.79	0.002
Multiple gestation	3.51	7.43–1.66	0.001
Resuscitation at birth	3	6.19–1.46	0.003
Blood transfusion (mL/kg)			
None	1		
< 45	1.07	4.16–0.28	0.92
> 45	4.91	17.83–1.35	0.02
Duration of oxygen therapy	3.11	7.32–1.32	0.009
Age of regaining birth weight	1.06	1.11–1.02	0.008

Table 4. Birth weight and gestational age of neonates with and without ROP

Characteristic	No ROP	ROP			Total
		Stage 1	Stage 2	Stage 3	
Birth weight (g)					
1500–1251	225 (91.1 %)	7 (2.8 %)	10 (4 %)	5 (2 %)	247 (59.7 %)
1250–1001	87 (76.3 %)	5 (4.4 %)	15 (13.2 %)	7 (6.1 %)	114 (27.5 %)
1000–751	30 (60 %)	1 (2 %)	11 (22 %)	8 (16 %)	50 (12.1 %)
≤ 750	1 (33.3 %)	1 (33.3 %)	0 (0 %)	1 (33.3 %)	3 (0.7 %)
Gestational age (w)					
≤ 28	54 (64.3 %)	3 (3.6 %)	14 (16.7 %)	13 (15.5 %)	84 (20.3 %)
32–29	226 (85 %)	11 (4.1 %)	21 (7.9 %)	8 (3 %)	266 (64.3 %)
36–33	59 (98.3 %)	0 (0 %)	1 (1.7 %)	0 (0 %)	60 (14.5 %)
≥ 37	4 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	4 (1 %)
Total	**343 (82.9 %)**	**14 (3.4 %)**	**36 (8.7 %)**	**21 (5.1 %)**	**414 (100 %)**

Table 5. ROP infants, with and without laser therapy

Characteristic	ROP/Laser (n = 33)	ROP/No laser (n = 38)	P-value
Birth weight (g)			0.69
> 1000	22 (44.9 %)	27 (55.1 %)	
≤ 1000	11 (50.0 %)	11 (50.0 %)	
Gestational age			0.004
> 28w	13 (31.7 %)	28 (68.3 %)	
≤ 28w	20 (66.7 %)	10 (33.3 %)	
Multiple plurality			0.73
Singleton	17 (48.6 %)	18 (51.4 %)	
Multiple	16 (44.4 %)	20 (55.6 %)	
ROP stage			< 0.001
1	0 (0.0 %)	14 (100 %)	
2	17 (47.2 %)	19 (52.8 %)	
3	16 (76.2 %)	5 (23.8 %)	

apnea, blood transfusion > 45 mL/kg, and oxygen therapy for > five days (Table 2), and by multiple regression analysis, birth weight (< 1000 grams), multiple pregnancy, resuscitation at birth, blood transfusion, duration of oxygen therapy, and age to regain birth weight were independent risk factors for ROP (Table 3).

On indirect ophthalmoscopy, ROP was detected in 71 infants (17.14 %); 3.4 % stage I, 8.7 % stage II, and 5.1 % stage III. ROP stages IV or V were not detected. Birth weight and gestational age as major risk factors of this group are presented in Table 4. Thirty-three patients with stages II and III ROP were treated with laser therapy, all of whom improved and none progressed to blindness. Birth weight, gestational age, multiple pregnancy, and stage of ROP of these infants are presented in Table 5.

Discussion

ROP is a major preventable cause of blindness in children throughout the world.[4] Since the recognition of ROP in 1942, three epidemics have been reported: the first was between 1940 – 1945 when oxygen therapy was identified as the major cause; the second was described during 1960 – 1970, when improved neonatal care in industrial countries led to increased survival of ELBW babies; and the third from 1980 up to date, as preterm babies of more than 32 weeks gestational age and a birth weight greater than 1500 grams continue to survive with the neonatal care available in developing countries with limited resources.

The prevalence of ROP varies greatly in different countries, with differing birth weights, gestational age, and risk factors. Accord-

ing to two major studies, CRYO Therapy-ROP (CRYO-ROP)[14] and ET-ROP,[15] 65.8 % to 68 % of newborns with a birth weight < 1250 grams develop some degree of ROP. Fielder and Reynolds report an overall rate of 5 % – 8 % ROP in developed countries, while a rate of 30 % has been reported from developing countries, but not many infants with ROP or blindness due to ROP are reported from very poor countries, because owing to lack of resources, most VLBW infants die before developing ROP.[16]

In our study, the rate of ROP was 17.14 % as compared to 10.45 % from the United States,[17] 29.2 % from Singapore,[18] 32.4 % from Pakistan,[19] 29 % from Kerman,[20] and 29.5 % from another study in Tehran.[21]

Studies have shown that the prevalence and the severity of ROP rise sharply in neonates with a birth weight of < 1000 grams. In Hiraoka, et al.'s study, 86.1 % of these tiny infants developed ROP and 41 % received laser therapy,[22] as compared to our figures of 41.5 % and 20.7 %, respectively.

We have addressed the salient risk factors for ROP; our findings compare well with those from other reports.[18,23] Similar to Blumenfield, et al.'s report,[24] multiple gestation was recognized as an independent risk factor for development of ROP in our patients as well, although the severity of ROP did not differ between babies delivered from a multiple gestation and singletons. In a study by Riazi- Esfahani, et al.[25] no significant difference in the rate or severity of ROP was seen between neonates born from multiple gestation and singletons in contrast to Motta, et al.'s study[26] which considers multiple gestation as a risk factor for development and severity of ROP.

Resuscitation at birth was noticed as another risk factor for ROP in our study; in Shah, et al.'s report[18] Apgar score < 5 ± 2 was named as one of the risk factors while in De Mauro, et al.'s research,[27] advanced resuscitation and in Peter, et al.'s study,[28] use of 100 % vs. 40 % oxygen for resuscitation were found to be related with ROP.

Blood transfusion has been recognized as increasing the risk of ROP in newborns; this effect has been attributed to increased delivery of oxygen, iron, and free radicals of oxygen to the retina.[29,30] Similar to our study, in Hesse, et al.'s paper, transfusion of > 45 mL/kg of blood was associated with an increased risk of ROP as opposed to lesser amounts.[31]

Duration of oxygen therapy was identified as an independent risk factor for ROP in Teoh, et al.'s study,[32] > 40 days in Niwald's cases,[33] > 30 days in Pinheiro, et al.'s infants,[34] and > seven days in Hakeem, et al.'s patients,[35] but this duration was > five days in our patients.

In studies by Wallace, et al.[36] and Wu, et al.[37] it was shown that low levels of insulin-like growth factor 1 (IGF-1) are associated with lack of optimal weight gain during the neonatal period and also aberrant development of the retina. This observation was considered so significant that Hellstrom, et al.[38] suggested replacing regular eye examination with repeatedly weighing the babies and checking IGF-1 levels. In our study, we used the days that the baby took to regain birth weight as a marker for risk of ROP. We observed that each one day delay in reaching the birth weight after 10 days increases the risk of ROP by 6 %. On the whole, using postnatal weight gain (till gestational age of 36 weeks) as a marker for predicting ROP needs further studies.[39]

As ROP leads to loss of eyesight in 3 % – 11 % of cases in developed countries and 11 % – 60 % of patients in the third world,[5] World Health Organization (WHO) recommends a three-pronged approach for management of this potentially preventable condition: elimination of preterm births, enhancement of neonatal care, and improvement in diagnosis and treatment.

Our study indicates that low birth weight, multiple gestation, resuscitation at birth, blood transfusion > 45 mL/kg, oxygen therapy for more than five days, and delay in regaining birth weight are the major risk factors for development of ROP in newborns. Therefore, a high index of suspicion, appropriate screening, prompt diagnosis, and early treatment will prevent the progression of ROP to blindness.

Acknowledgments

We would like to thank the director and the personnel of Pediatric Infections Research Center for their support in the implementation of this study. We also thank all our colleagues (physicians, nurses, and other personnel) in the Newborn Service of Mahdieh Hospital for their help in caring for the patients, collection and documentation of data, and advising the study team.

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