Original Article

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Impact of Birth and Hospitalization Factors in Retinopathy of Prematurity

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Abstract

Background: Retinopathy of Prematurity (ROP) is a pathologic condition in the retina characterized by abnormal vasoproliferation. We aim to investigate the correlation of different birth- and hospitalization-related factors in the progression of ROP.

Methods: This historical cohort study performed in the ophthalmology center of Ayatollah Rouhani Hospital in Babol (Babol University of Medical Sciences, Babol, Iran), included 828 infants (gestational age <35 weeks and birth weight <2500 *g*). Also, data were collected from the history of hospitalized premature infants.

Results: The lower gestational weight of infants has been observed in ROP infants (1418.05±547.09 *g*) compared to non-ROP infants (1917.31±486.01 *g*) ($p<0.001$). In addition, the average gestational age of ROP infants (30.28±2.34 weeks) was younger than non-ROP infants (33.26±1.00 weeks) ($p=0.042$). Increase in the duration of hospitalization increased 6% the chance of ROP in infants (OR=1.06; 95%CI: [1.05,1.08]) ($p<0.001$). Furthermore, increase in the count of blood replacement decreased 29% the chance of complete remission of ROP (OR=0.71; 95%CI: [0.51,0.95]) ($p=0.029$). The blood group does not have an impact on ROP development or remission.

Conclusion: More birth weight of premature infants is associated with less chance of ROP incidence. Moreover, the lower gestational age is related to more chances of ROP.

Keywords: Hospitalization, Infant, Premature infant, Retinopathy of prematurity

Introduction

Retinopathy of Prematurity (ROP) is an infantile retinal disease corresponding to lifetime visual impairment and blindness (1,2). ROP affects over 33% of premature infants (3). ROP is characterized by abnormal intravitreal neovascularization in the premature retina (4-6). ROP is created by abnormal intravitreal neovascularization in the developing retina. ROP is a multifactorial disease resulting in genetic disorders and environmental conditions. A profound investigation of ROP infants establishes the role of different factors in the progression of ROP. The identification of risk factors helps the prevention of the progression of ROP (7).

Some general risk factors affect fetal diseases, *i.e.,* placental and fetal problems (8,9). Also, studies show that some irrelevant conditions may affect fetal diseases, *i.e.,* sex, blood group, days of hospitalization of infants, count of blood replacement (in required cases), type of delivery, CPR requirement, surfactant requirement, and phototherapy requirement (10-12). In this blinded study, we investigated the impact of the general parameters as potential factors of ROP such as gestational weight, gestational age, duration of hospitalization, count of blood replacement, sex, blood group, type of delivery, Cardio-Pulmonary Resuscitation (CPR) requirement, surfactant requirement, and phototherapy.

Materials and Methods

This historical cohort study was performed in the Ophthalmology and NICU departments of Ayatollah Rouhani Hospital in Babol (Babol University of Medical Sciences, Babol, Iran) and included 828 infants (303 ROP infants as cases and 525 non-ROP infants as controls). Institutional ethics committee approval was obtained from the Local Ethics Committee (IR.MUBABOL.REC.1399.373). Initial examinations were performed one hour after the administration of 2.5% phenylephrine and 0.5% tropicamide and funduscopic examinations implemented by using a binocular indirect ophthalmoscope, 28D lens, scleral depressor, and pediatric speculum in the NICU department. In case there was an ROP, the regular follow-up examinations were continued until complete remission was achieved (defined as complete retinal vascularization and regression of ROP). In addition, treatment protocol, including anti-vascular endothelial growth factor injection, was conducted according to the International Classification of Retinopathy of Prematurity (ICROP) criteria for stage III ROP patients. The infants were separated into two groups: the infants with no signs of ROP as the control group and infants with different stages of ROP as the case group.There was only stage 1, 2, and 3 of ROP in patients and none of the infants had stages 4 and 5.

The inclusion criteria included the age of <35 weeks, birth weight <2500 *g*, and conscious parental consent. The exclusion criteria were the age of over 35 weeks, birth weight of more than 2500 *g*, and secondary ophthalmic conditions.

Statistical analysis was performed using the SPSS 21.0 software. Quantitative variables were reported with mean±SD. Chi-square and independent T-test were utilized to evaluate univariate comparisons of risk factors between the groups. The level of significance was taken to be $p<0.05$ for all statistical tests.

Results

The impact of effectors on the incidence of ROP

The lower gestational weight of infants has been observed in ROP infants (1418.05±547.09 *g*) compared to non-ROP infants (1917.31±486.01 *g*) ($p<0.001$). Also, the average gestational age of ROP infants (30.28±2.34 weeks) was younger than non-ROP infants (33.26±1.00 weeks) ($p=0.042$). Mean±SD of days of hospitalization was higher in ROP infants (31.69±21.11 days) compared to non-ROP infants (14.67±13.36 days) ($p<0.001$) (Table 1). There was no significant correlation between ROP incidence and sex, blood group, type of delivery, CPR requirement, surfactant requirement, and phototherapy requirement in infants.

The investigation of odds ratio of effectors on ROP shows that the increase in gestational age decreased 40% the chance of ROP in infants (OR=0.6; 95%CI: [0.56,0.65]) (<0.001). In addition, increase in the duration of hospitalization increased 6% the chance of ROP in infants (OR=1.06; 95%CI: [1.05,1.08]) (<0.001). Intrauterine growth restriction (IUGR) decreased 67% the chance of ROP in infants (OR=0.33; 95%CI: [0.17,0.64]) (<0.001) (Table 2).

Table 1. Correlation of ROP (diagnosed in the first examination) and clinical/paraclinical data

Name	Level	Total	Non-ROP infant (n=525)	ROP infant (n=303)	p-value
Gestational weight (g)		1788.35±567.54	1917.31±486.01	1418.05±547.09	**<0.001**
Gestational age (weeks)		32.17±6.95	33.26±1.00	30.28±2.34	**0.042**
Days of hospitalization (day)		19.29±17.96	14.67±13.36	31.69±21.11	**<0.001**
Count of blood replacement		1.10±5.26	1.32±7.53	1.27±1.44	0.925
Sex	Female	377 (45.81%)	242 (46.1%)	135 (45.3%)	0.808
	Male	446 (54.19%)	283 (53.9%)	163 (54.7%)	
Blood group	A+	115 (26.62%)	76 (26.95%)	39 (26%)	0.242
	A-	7 (1.62%)	7 (2.48%)	0 (0%)	
	B+	103 (23.84%)	70 (24.82%)	33 (22%)	
	B-	10 (2.31%)	7 (2.48%)	3 (2%)	
	O+	150 (34.72%)	90 (31.91%)	60 (40%)	
	O-	14 (3.24%)	12 (4.26%)	2 (1.33%)	
	AB+	29 (6.71%)	18 (6.38%)	11 (7.33%)	
	AB-	4 (0.93%)	2 (0.71%)	2 (1.33%)	
Type of delivery	Normal vaginal delivery	74 (17.49%)	43 (17.06%)	31 (18.13%)	0.809
	Cesarean delivery	349 (82.51%)	209 (82.94%)	140 (81.87%)	
CPR requirement	No	69 (32.86%)	44 (36.97%)	25 (27.47%)	0.170
	Yes	141 (67.14%)	75 (63.03%)	66 (72.53%)	
Surfactant requirement	No	8 (3.59%)	5 (4.5%)	3 (2.68%)	0.238
	Yes	213 (95.52%)	104 (93.69%)	109 (97.32%)	
	Missed data	2 (0.9%)	2 (1.8%)	0 (0%)	
Phototherapy	No	7 (2.9%)	4 (2.4%)	3 (4.05%)	0.849
	Yes	224 (92.95%)	156 (93.41%)	68 (91.89%)	
	Missed data	10 (4.15%)	7 (4.19%)	3 (4.05%)	

The impact of effectors on complete remission of ROP

The results of the impact of effectors on complete remission of ROP show that higher gestational age increases the chance of complete remission of ROP by about 21% in ROP infants (OR=1.21; 95%CI: [1.08, 1.36]) (p<0.001). Moreover, increase in the count of blood replacement decreased 29% the chance of complete remission of ROP (OR =0.71; 95%CI: [0.51, 0.95]) (p=0.029) and more time on hospitalization reduced 2% (OR=0.98; 95%CI: [0.96, 0.99]) (p=0.004) the chance of complete remission of ROP in ROP infants. Other factors, *e.g.,* blood groups, did not affect the chance of complete remission of ROP (Table 3).

The impact of effectors on remission of ROP in terms of the stage and zone

The results of Bayesian Logistic regression show that none of the factors affect the stage of ROP (reduction of the stage of ROP) and deterioration of the zone of ROP (reduction of the zone of ROP) between two examinations (Tables 4 and 5).

Discussion

ROP is a vasoproliferative retinal disease in premature

Table 2. Odds ratio of effectors in ROP incidence

Factors		OR (95% CI)	p-value
Gestational age		0.6 (0.56,0.65)	**<0.001**
Blood group	A-	0.1 (0.01,1.79)	0.117
	B+	0.93 (0.54,1.63)	0.805
	B-	0.86 (0.24,3.28)	0.827
	O+	1.31 (0.8,2.14)	0.277
	O-	0.38 (0.09,1.5)	0.167
	AB+	1.2 (0.54,2.7)	0.665
	AB-	1.69 (0.3,10.24)	0.552
Count of blood replacement		1 (0.95,1.04)	0.939
CPR requirement		1.55 (0.86,2.82)	0.147
Days of hospitalization		1.06 (1.05,1.08)	**<0.001**
Fetal problem		1.39 (0.94,2.08)	0.102
Placental problem*	Decollement	1.57 (0.57,4.31)	0.38
	Placenta previa	8.4 (0.39,165.34)	0.165
	IUGR	0.33 (0.17,0.64)	**<0.001**
Surfactant requirement*	No	1.83 (0.49,6.82)	0.377
	Yes	0.25 (0.01,6.36)	0.395
Type of delivery		0.93 (0.56,1.56)	0.777
Phototherapy	No	0.58 (0.12,3.02)	0.485
	Yes	0.57 (0.07,4.43)	0.587
Sex (male)		1.03 (0.78,1.37)	0.826
Gestational weight		1 (1,1)	**<0.001**

* Calculated by Bayesian Logistic regression due to data sparsity.

infants. ROP is the major cause of lifetime visual impairment and blindness at an early age. ROP is a multifactorial disease, and a large number of studies have been conducted to analyze the relationship between pathogenesis of ROP and risk factors such as low birth weight, short gestational age, hypoxia, and other factors. Also, several factors involving birth conditions and infantile problems are associated with ROP progression. In this study, the role of different factors were investigated in terms of birth conditions and infantile problems of ROP infants.

The higher gestational weight of infants has been observed in non-ROP infants (1917.31±486.01 *g*) compared to ROP infants (1418.05±547.09 *g*) ($p<0.001$). This result reveals that ROP is more progressed in more prematurity conditions. In other words, less weight of infants is more common in ROP infants. This condition is probably due to less completed development of the retina and less vascularization to oxygen delivery. In a study conducted by by Eckert *et al*, it has been shown that less bodyweight is a predictor of any stage and severe ROP (13). Also, in a study by Aydemir *et al*, poor weight gain for birth weight was considered as a predictor of ROP (14). Due to these results, a completed nutrition therapy might be suitable for mothers to more weighting of infants. Regarding this hypothesis, a meta-analysis study by Vayalthrikkovil *et al*, parenteral administration of fish-oil lipid emulsions significantly reduced the incidence of

Table 3. Effect of different factors to increase or decrease complete remission chance of ROP

Factors		OR (95% CI)	p-value
Gestational age		1.21 (1.08,1.36)	**0.001**
Blood group*	A-	1.01 (0.01,132.03)	1
	B+	1.8 (0.65,5.05)	0.271
	B-	0.37 (0.05,2.83)	0.349
	O+	0.66 (0.29,1.49)	0.329
	O-	3.69 (0.18,75.68)	0.403
	AB+	0.57 (0.15,2.2)	0.402
	AB-	3.74 (0.18,81.32)	0.403
Count of blood replacement		0.71 (0.51,0.95)	0.029
CPR requirement		0.75 (0.26,2.03)	0.579
Days of hospitalization		0.98 (0.96,0.99)	0.004
Fetal problem		1.31 (0.74,2.52)	0.378
Placental problem	Decollement	1.82 (0.38,12.84)	0.481
	Placenta Previa	0.73 (0.03,18.5)	0.822
	IUGR	0.73 (0.2,2.67)	0.62
Surfactant requirement*	No	0.14 (0.01,2.8)	0.194
	Yes	1.03 (0.01,131.34)	1
Type of delivery		0.42 (0.17,0.97)	0.052
Phototherapy	No	0.59 (0.03,6.42)	0.669
	Yes	1 (0.02,40.4)	1
Sex		0.65 (0.39,1.05)	0.082
Gestational weight		1 (1,1)	<0.001

* Calculated by Bayesian Logistic regression due to data sparsity.

severe ROP and laser therapy requirement (15). Furthermore, a study by Lenhartova *et al* showed that providing enough nutrients for infants in the pregnancy period and early enteral feeding breast milk of their own mother leads to a significant reduction in the severity of ROP (16). Upadhyay *et al* stated that infants receiving early optimal nutrition therapy had less incidence of ROP (17).

Mean±SD of days of hospitalization was higher in ROP infants (31.69±21.11 days) compared to non-ROP infants (14.67±13.36 days) (p<0.001). It seems that days of hospitalization are an independent but significant correlated factor to the progression of ROP that refers to a worse condition of premature infants, which is related to more prevalence of ROP.

Also, the average gestational age of ROP infants (30.28±2.34 weeks) was younger compared to non-ROP infants (33.26±1.00 weeks) (p=0.042). Contrary to the result, Wu *et al* showed that less gestational age is associated with a healthy state in terms of ROP (18). It seems that gestational age requires more studies to the identification of its role in ROP progression. In the investigation of infant problems, the results show that Intrauterine Growth Restriction (IUGR) decreases 67% the chance of ROP in infants, while Nong *et al* failed to find any association between IUGR and ROP (19). There is no other study on the impact of IUGR in ROP.

The results of the current study show that the increase in the count of blood replacement decreased 29%

Table 4. Effects of the different factors on decreasing the stage of ROP (revealing the ROP in terms of the stage)

Factors		OR (95% CI)	p-value
Gestational age		1.04 (0.79,1.39)	0.804
Blood group*	A-	0.97 (0.01,132.73)	1
	B+	2.59 (0.1,60.74)	0.56
	B-	1.55 (0.04,62.28)	0.809
	O+	0.27 (0.04,1.77)	0.177
	O-	1.01 (0.01,138.07)	1
	AB+	2.18 (0.07,62.85)	0.639
	AB-	1 (0.01,148.41)	1
Count of blood replacement		0.82 (0.51,1.34)	0.396
CPR requirement*		0.35 (0.01,8.44)	0.520
Days of hospitalization		0.98 (0.94,1.02)	0.233
Fetal problem		1.11 (0.29,18.55)	0.906
Placental problem*	Decollement	1.72 (0.05,60.88)	0.764
	Placenta previa	1.39 (0.03,65.32)	0.862
	IUGR	2.44 (0.11,58.13)	0.564
Type of delivery		3.47 (0.43,20.62)	0.187
Phototherapy*	No	0.57 (0.01,20.94)	0.772
	Yes	1.25 (0.02,83.46)	0.904
Sex (male)		0.76 (0.15,3.04)	0.704
Gestational weight		1 (1,1)	0.979

* Calculated by Bayesian Logistic regression due to data sparsity.

the chance of complete remission of ROP (p=0.029). This result established that the requirement for blood replacement, which is an indicator of the blood-related disease, is associated with ROP progression. In other words, the less requirement of blood replacement promises a better prognosis for ROP. Moreover, there is no difference between the different blood groups and the chance of ROP incidence.

Conclusion

In this study, it was found that the lower gestational weight, the lower gestational age, and the increased duration of hospitalization are associated with an increased chance of ROP. Also, an increase in the count of blood replacement decreases the chance of complete remission of ROP. To continue, we recommend studying more ROP infants and investigating the effect of underlying diseases on ROP in premature Iranian infants to introduce a novel prognostic marker for ROP. Indeed, the results of our study and correlated studies help more suitable medical care for ROP infants to prevent their disease-related disabilities.

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Conflict of Interest

There is no conflict of interest in this manuscript.

Table 5. Effect of the different factors on decreasing the zone of ROP (deterioration of ROP in terms of the zone)

Factors		OR (95% CI)	p-value
Gestational age		1.12 (0.91,1.4)	0.3
Blood group	B+	0.12 (0.01,1.25)	0.103
	B-	0.09 (0,3.43)	0.173
	O+	0.19 (0.01,1.27)	0.145
	AB+	0.36 (0.01,10.68)	0.508
Count of blood replacement		0.95 (0.63,1.48)	0.815
CPR requirement		1.28 (0.15,8.34)	0.801
Days of hospitalization		0.98 (0.96,1.01)	0.237
Fetal problem		0.42 (0.13,1.22)	0.112
Placental Problem	Decollement	2.23 (0.09,57.33)	0.622
	Placenta previa	1.73 (0.05,59.34)	0.767
	IUGR	0.38 (0.07,2.15)	0.279
Type of delivery		1.36 (0.18,6.92)	0.725
Phototherapy	No	3.62 (0.25,52.37)	0.354
	Yes	3.52 (0.1,121.85)	0.484
Sex		0.81 (0.28,2.17)	0.679
Gestational weight		1 (1,1)	0.28

* Calculated by Bayesian Logistic regression due to data sparsity.

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