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Evaluation of Prevalence and Severity and Risk Factors of Retinopathy Prematurity in Premature Infants in Ilam

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A B S T R A C T

Introduction: Retinopathy of prematurity (ROP) is a retinal proliferative vascular disorder of premature infants. In spite of improvement in the management of neonatal disorders, ROP is one of the leading causes of blindness in premature infants in the world. Present screening of ROP first is based on risk factors of birth weight and gestational age. Nevertheless, some authors believe that other risk factors, including maternal and perinatal factors and nutrition and genetics, are effective too. Nevertheless, we decided to study risk factors of ROP in neonates.

Materials & Methods: This cross-sectional study on the population of neonates born in Ilam hospitals during 2012-2018. In this study we evaluated ROP in premature infants that were hospitalized in Ilam hospitals.

Results: Altogether, 627 infants were evaluated, among them 332 boys and 295 girls. For the mean of birth weight between them, there was a significant difference (P-value=0.001). In addition, gestational age according to sex had a difference; in girls it was less than boys, and it was statistically significantly different (P-value=0.001). ROP was found to be significantly more prevalent in girls compared to boys. Prevalence of ROP among girls and boys was 27.8% and 15.7%, respectively. The prevalence of retinopathy in two sexes was 18.7%.

Conclusion: Among these factors, birth weight, gestational age, blood transfusion history, PDA, and asphyxia had statistically significant differences with the occurrence of ROP. The best way to avoid the progression of ROP is screening and examination and timely treatment of this disorder.

Keywords: Premature Neonates, ROP, Risk Factors

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Introduction

ROP is one of the common causes of blindness in childhood. When ROP was explained in the decade of 1940 for the first time, three stages of the epidemic of ROP had been observed in the world (1). In spite of progress in neonatal care, ROP occurrence and its related visual problems all over the world are progressing, and their control is problematic (2). Retinopathy of prematurity, also called retrolental fibroplasia, is a Vaso proliferative disease in the developing retinal vessel of premature infants (3). It results in different outcomes, varying from normal vision to blindness. In the United States of America, after visual cortex disorders, it is a common cause of blindness in children, and in developing countries, it is a leading cause of blindness too (4). ROP is a disorder that is involved in 65% of premature infants (under gestational age of 37 weeks) with low birth weight that results in blurred vision or even blindness in a great number of affected patients. The incidence rates of this disorder among infants with low birth weight in different countries are 10-46%, and in Iran 6-12%have been reported (5, 6).

ROP is classified according to severity into 5 stages and, 6-12% have according to area of retinal vascularization into three zones. Even in infants with mild ROP that improved without sequelae, it is more probable to have myopia, strabismus, and amblyopia than normal infants (7). Low gestational age and low birth weight are essential risk factors of retinopathy of prematurity occurrence. Because retinal vascularization completion in term neonates is an obstacle for disease creation (8). Factors that damage the vascularization process can facilitate retinopathy of prematurity in neonates. They include multiple causes such as prolonged hyperoxia, shock, asphyxia, acidosis, vitamin E deficiency, hypo- and hypercarbia, race, preeclampsia history in the mother, multiple transfusions, PDA, intraventricular hemorrhage, bronchopulmonary dysplasia, and a history of beta blockers in the mother.

The incidence rates of this disorder among infants with low birth weight in different countries are 10-46% (9), and in Iran, 6-12% (10) have been reported. In spite of the progress that has occurred in the prophylaxis, screening, and treatment of retinopathy of prematurity in the world and considering its spontaneous improvement, ROP annually leads to 400 cases of blindness and 4300 cases of serious retinal scars and complications such as cataracts, glaucoma, and amblyopia (11). Investigations demonstrate that a delay in diagnosis is associated with a decrease of vision or visual loss (12). Thus, immediate diagnosis increases the success rate of treatment and decreases the complication of illness (13). Accordingly, we decided to study the prevalence rate and risk factors affecting this illness in premature neonates born in hospitals of Ilam.

Materials and methods

Study Design

This study was done as population-based cross-sectional study. Data was gathered in medical files and registered in a check list. All of premature neonates hospitalized in NICU department of ayatollah taleghani hospital of Ilam that have been examined for ROP during 2012-2018 entered.

Setting and Participants

Inclusion and exclusion criteria: Inclusion criteria included premature infants with risk factor include premature infants under 32 weeks especially under 30 weeks, premature infants under 1500 g spaciously under 1250 g, and premature infants that have risk factors such as oxygen therapy, hypoxia, hypercarbia and underlying disease. Exclusion criteria included infants that have no inclusion criteria and infants because of corrupted files we couldn’t retinopathy in them.

Sample Size

All eligible neonates during the study period were included; therefore, no a priori sample size

calculation was performed, and the sample size was determined by census sampling.

Measurements & Validity and Reliability

A comprehensive examination for screening was done by an expert ophthalmologist. A binocular indirect ophthalmoscope and a 20-diopter lens following the application of a pharmacological myderiatic agent and topical anesthesia was used by ophthalmologist. ROP classification was based on the international classification of ROP(ICROP).

Statistical and Data Analysis

In study. the SPSS version 26.0(SPSS Inc., Chicago, Illinois, USA) was used for analyses of data. Descriptive statics are expressed in absolute and relative frequency for qualitative variables, as well as in mean and standard deviation for quantitative variables. All variables had normal distribution and binary logistics regression test was utilized. To identify and quantify the association between potential risk factors and the development or severity of ROP, we employed both univariate logistic regression analyses.

In the univariate regression analysis, each independent variable was analyzed separately against the outcome variable (presence or severity of ROP), allowing us to screen for factors potentially associated with ROP without adjusting for confounding influences. Variables showing statistically significant associations at a predefined threshold (commonly $p < 0.1$) in univariate analysis were then entered into a multivariate logistic regression model. The multivariate analysis adjusts for the simultaneous effects of all included variables. Qualitative variables were also analyzed by the Chi-square and Fisher Exact test. P-value<0.05 were considered significant level.

Results

Overall, 627 neonates were evaluated; among them, 332 subjects were male and 295 subjects were female. The mean birth weights of males and females were statistically significantly different. Birth weight of females was less than males. (P-value=0.001) (table 1). Also, gestational age between males and females was different; gestational age of females was less than males and was statistically significantly different. (P-value=0.001) ROP in females was greater than in males (Table 1). In this study the relation of paternal educational and occupational level and job with ROP wasn't statistically significant. But the relationship of place of residence with ROP was statistically significant. This demonstrated that infants of rural families are significantly more likely than urban families to result in ROP. In this study the educational level, employment, and place of residency of parents were evaluated. In relation to occupation, near 88% of mothers were housekeepers, and near 71% of fathers were free in their jobs. In relation to education, 5.1% of fathers and 4.8% of mothers had a high educational grade.

Table 1. Demographic and clinical characteristics of participants.

variable	ROP(n=121)	NON-ROP(n=506)	p-value
Birth weight(g)*	1515(440)	2364 (577)	<0.001
Gestational age *	30 (2.0)	34 (2.0)	<0.001
Infection history	48(53.0%)	41(46.1%)	<0.001
O_2therapy history	112(19.0%)	454(80.0%)	<0.001
Multiple gestation	77(17.0%)	375(82.0%)	0.017
Pulmonary distress	114(22.0%)	384(77.0%)	<0.001
phototherapy	96(30.0 %)	215 (69.0 %)	<0.001
Ventricular hemorrhage	21(50.0 %)	21 (50.0%)	<0.001
Apnea	84(42%)	112(57.0%)	<0.001
Sepsis	48 (53.0%)	41 (46.1%)	<0.001
PDA	25 (32.0%)	51 (67 %)	<0.001

asphyxia	6 (20.0%)	24 (80.0%)	<0.001

* Mean ± Standard deviation ~~D~~

In this study the severity of ROP in both sexes was evaluated and compared (table 3). The incidence of ROP in females was greater than in males, 27.8% and 15.7%, respectively; the total (both sexes) incidence was 18.7% (Table 2).

Table 2. severity and incidence of ROP in both sexes.

Severity of retinopathy	Incidence of retinopathy of prematurity					
	boy		girl		both	
	number	incidence	number	incidence	Number	incidence
Stag 1 zone 1	19	5.7	15	5.1	34	5.4
Stage 1 zone 2	12	3.6	22	7.5	34	5.4
Stag1 zone1 without plus	8	2.4	3	1.0	20	3.2
Stage1 zone2 without plus	2	0.6	12	4.1	2	0.3
Stage1 zone3 without plus	2	0.6	15	5.1	6	1.0
Stag2 zone 1 without plus	1	0.3	1	0.3	3	0.5
Stage2 zone 2	1	0.3	5	1.7	16	2.6
All	52	15.7	82	27.8	117	18.7

Table 3. univariate regression models analysis of relation of risk factors with ROP.

Variable	Odds Ratio (95% CI)	p-value
Sex	1.15(0.07-1.65)	0.709
Birth weight	0.421(0.36-0.48)	0.001
Gestational age	0.83(0.76-0.88)	0.001
Transfusion history	0.42(0.20-0.88)	0.022
Infection history	1.94(0.82-4.60)	0.141
O_2 therapy	1.66(0.60-3.52)	0.322
Multiple gestation	1.10(0.70-1.70)	0.752
Pulmonary distress	0.83(0.60-1.15)	0.755
Apgar min 1	1.00(0.99-1.01)	0.95
Apgar min 5	0.60(0.59-0.62)	0.001
phototherapy	0.54(0.28-1.05)	0.071
Ventricular hemorrhage	1.06(0.70-1.60)	0.853
apnea	0.81(0.60-1.13)	0.568
sepsis	0.28 (0.12-0.65)	0.006
PDA	2.54(1.08-5.90)	0.033
asphyxia	8.699(1.90-15.2)	0.005

In this study birth weight and gestational age, transfusion history and 5-minute Apgar score, sepsis, PDA, and asphyxia were statistically significant based on univariate analysis. However, univariate analysis revealed a significant relationship between asphyxia, PDA, and ROP. Specifically, asphyxia increased by an average of 8.69 points (P = 0.005) (Table 3).

Discussion

In this study, the incidence and risk factors of ROP in Ilam were evaluated. Neonatal characteristics such as birth weight, gestational age, transfusion history, oxygen therapy, multiple gestation, pulmonary distress, Apgar score (1 & 5 minutes), and phototherapy. Intraventricular hemorrhage. Apnea. Sepsis, PDA, asphyxia, and their relation with ROP using logistic regression were evaluated. Among them, birth weight, gestational age, transfusion history, 5-minute Apgar, sepsis, PDA, and asphyxia with the occurrence of ROP were

statistically significant. These findings were consistent with a study that was done by Aezami et al. In this study gestational age under 32 weeks, birth weight under 1500 g, arterial O_2 saturation over 50%, sepsis, respiratory distress syndrome, intraventricular hemorrhage, use of ventilator, apnea, use of transfusion, use of oxygen, and phototherapy were reported as the uppermost risk factors of ROP (14).

The prevalence of ROP in our study was 18.7%. Prevalence of ROP in countries with high socioeconomic status is different. In the Middle East (neighboring countries of Iran), different prevalence has been reported; it is different from 15% to 32%. (15-18) This difference is observed in European countries too. Because incidence of ROP in their studies of 9-72% has been reported. In addition to gestational age and birth weight, this difference can be attributed to differences in the number and percent of premature infants that have survived in different areas (19). For example, in a survey (1999-2000) in Austria, 67% of neonates born at gestational ages of 22-26 weeks have survived (20). While in a study of premature neonates with gestational ages of 24-26 weeks born in Tehran, 4% was reported. In other words, comparisons of the prevalence of ROP in premature infants between Iran and other countries are challenging (21). Despite this, many countries have shown an increased rate of ROP during the past two decades. A study in the USA has reported an increased incidence of ROP from 14.7% in the year 2000 to 19.9% in 2012 (22). Another study in England reported that every degree of ROP in neonates less than 1500 grams has increased from 1.3% in 1999 to 12.9% in 2011. This is attributed to the increased rate of survival of premature infants and the compilation of instruction for screening and treatment of ROP (23). All of these data are consistent with studies in Iran.

In a study in Sweden, ROP was reported as the most underlying cause of blindness. It was found that 24% of infants born during 1998-2008 were affected (24). In another study in the USA, ROP as a second cause of visual impairment (11.8%) was introduced. In this study cortical visual impairment was reported as a second cause (24.9%) after ROP (25). Another study in Norway reported neuro-ophthalmic impairments (such as CVI) as a common cause (37.3%) of visual impairments in children and adolescents, while retinal impairments (such as ROP) were responsible for 19.1% of cases (26).

Limitations and Strengths

The study is strong in that it has a relatively large referral sample size, including hundreds of cases of retinopathy of prematurity, which has increased the accuracy of prevalence estimates and has also identified local risk factors such as low gestational age and low birth weight, which are consistent with national data, useful for improving screening policies. However, the retrospective design reduces control over variables and increases the possibility of selection bias, and the focus on referred infants (and not all preterm infants in the region) has led to an overestimation of prevalence and reduced generalizability of the results; in addition, the incomplete reporting of disease severity stages (stages 1 to 5) and the lack of information on protective factors or regionally specific data are other important limitations of the study.

Conclusion

Retinopathy of prematurity is a common eye disease among premature infants. Respiratory problems of the newborn, low birth weight, low maternal age, and high-pressure supplemental oxygen are factors that contribute to retinopathy. If the disease progresses, the retina will detach over time, and the baby will lose his vision forever. For this reason, timely diagnosis and screening at birth are of great importance.

In the past few decades, neonatal care has developed significantly. However, ROP is still the leading cause of childhood visual impairment worldwide.

Understanding the heterogeneity of the ROP epidemics worldwide is essential to reduce this significant global burden. The most important aspect in the prognosis of ROP is to prevent it from progressing to an advanced stage, and in an effort to make it more efficient, the ROP classification system has been developed and revised. Treatment options developed or in development to date include cryotherapy, laser ablation, surgical treatment, and anti-VEGF therapy.

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CRediT authorship contribution statement

Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Software, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: SN, ES, ZP.

Declaration of Generative AI and AI-assisted technologies in the writing process

The author states that they have no relevant or substantial financial interests in the research discussed in this work.

Conflict of interest

There is no interest conflict.

Ethical considerations

This study was retrospective study that extracted data from medical files and only data was evaluated and personal characteristics of patients wasn’t evaluated and were considered confidential and no extra cost were imposed on them (IR.MEDILAM.REC.1404.034).

Data availability statement

The datasets utilized and/or analyzed in the present study are obtained from the corresponding author upon reasonable request.

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