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Original Article

Evaluation of Risk Factors for Retinopathy of Prematurity in Preterm Neonates

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ABSTRACT

Background: The most common cause of preventable blindness in children is retinopathy of prematurity (ROP). The most important risk factors for this disease are preterm delivery and low birth weight (LBW). This research was performed to evaluate the prevalence of and risk factors for ROP in preterm neonates.

Methods: Our research was a cross-sectional descriptive and retrospective study conducted on preterm neonates in the Neonatal Intensive Care Unit (NICU) of Mahdieh Hospital in Tehran, Iran, in 2015. All neonates with a gestational age of < 32 weeks and birth weight of < 1,500 g were enrolled. Demographic data and risk factors for ROP were evaluated. Statistical analysis was conducted by SPSS (version 20) with a 95% confidence interval and. P-value less than 0.05 was considered statistically significant.

***Results*:** Our study was conducted on 154 patients. Mean gestational age and birth weight of the newborns were 28.69±1.82 weeks (range: 23-32 weeks) and 1114.94±240.982 g (range: 550-1500 g). The ROP was detected in 76 (49.4%) patients, 55.26%, 34.2%, and 10.53% of whom had stages I, II, and III of ROP. Stages IV and V were not seen in our patients. The incidence of ROP was significantly affected by low gestational age and birth weight, delivery room resuscitation, prolonged oxygen therapy and mechanical ventilation, and repeated packed cell transfusion.

Conclusion: Despite the improvement in the care of preterm infants in the NICUs, the prevalence rate of ROP was high. Therefore, it is critical to adopt better care for disease prevention, timely screening, and appropriate treatment programs for the neonates who are at the risk of this disease.

Keywords: Infant, Oxygen therapy, Premature, Retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a disorganized retinal blood vessel growth in the preterm neonates survived in the neonatal intensive care units (NICUs). This disease can cause blindness or visual impairment in case of the lack of timely diagnosis and treatment. The most common cause of preventable blindness in children is ROP (1-5). Despite the decrease in the mortality rate of extremely preterm infants in NICUs worldwide, their morbidities, such as ROP, is increasing, especially in developing countries (6-9).

The overall prevalence of the disease is about 50% in the preterm infants with a birth weight of < 1,250 g (10). In spite of the lower survival rate of extremely premature infant in developing countries, the rate of ROP is much higher. The rate of disease declines with the enhancement of gestational age. The most important risk factors for ROP are preterm delivery and low birth weight (11, 12).

All severely premature neonates, particularly sick newborns with prolonged mechanical ventilation and oxygen therapy, are at the risk of this complication. This disease has multifactorial causes, such as surfactant therapy, wide variations

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of blood pressure, oxygen and CO_2 levels in the circulation, persistent hyperoxia and hypoxia, sepsis, packed cell transfusion, intraventricular hemorrhage, bronchopulmonary dysplasia, fungal infections, erythropoietin usage, hyperglycemia during hospital stay, insulin therapy, low caloric intake, and poor weight gain (4, 12-17). It is revealed that breastfeeding, in addition to other benefits for the baby, reduces the incidence of ROP in premature neonates (18).

Due to the toxic effects of oxygen in the maturity of retinal vessels, oxygen therapy is one of the most important risk factors for ROP in the preterm neonates who are prone to respiratory failure arising from surfactant deficiency and pulmonary immaturity that necessitate the use of oxygen as a vital element for life saving and prevention of hypoxic-ischemic encephalopathy. The safe level of oxygen therapy is not specified (10).

The ROP is initiated as an arrest of normal retinal (neuronal and vascular) development in preterm neonates (11, 19-22). Cessation of the normal vascularization of the retina and abnormal neovascularization increase the susceptibility of retinal detachment and blindness or visual impairments in premature newborns (11, 23). Based on the international classification of ROP in 1984 and its revision in 2005 (24), this disease is categorized into three zones (1-3) based on the area of the affected retina. The ROP located in the most immature zone 1 has the worst prognosis, and the disease in zone 3 has better outcomes.

Based on the degree of vasculopathy at the vascular transition, it is divided into 5 stages (1-5) with the progression of disease from stage 1 to 5, which has the most advanced degree of disease (24, 25). Screening of preterm neonates in the NICUs with ophthalmological examinations by an expert ophthalmologist can reveal the disease in early stages. Interventions, such as laser photocoagulation therapy or injection of anti-vascular endothelial growth factor (anti-VEGF) therapy, prevent the progression of the disease (26, 27).

In extremely preterm neonates, the elimination of disease is not possible because even the breathing of air without an excessive amount of oxygen can be dangerous for an immature retina (28, 29). Good care of these vulnerable patients can decrease disease incidence or reduce its severity. With regard to the multifactorial nature of ROP, this research was conducted to evaluate the recent prevalence of and risk factors for this disease in the NICU of Mahdieh Hospital in Tehran, Iran.

Methods

This cross-sectional descriptive, retrospective study was conducted on preterm neonates admitted to the NICU of Mahdieh Hospital in 2015. The hospital under investigation was a maternity hospital with an annual delivery rate of 4,000-5,000 neonates. All preterm neonates with a gestational age of < 32 weeks and birth weight of < 1,500 g undergoing an ophthalmologic examination for the screening of ROP were included in our research. The neonates with multiple anomalies or those receiving no follow-up for visual evaluation were excluded.

Based on the policy of our NICU, all preterm neonates with the gestational age of < 34 weeks regardless of their clinical course, as well as the sick preterm newborns with the gestational age of 34-37 weeks and birth weight of < 2,000 g were examined by an expert ophthalmologist at the postnatal age of 4 weeks. Our research was performed based on the guidelines of the Declaration of Helsinki and the approval of the Institutional Review Board of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Furthermore, written informed consent of parents was obtained.

The demographic and clinical data recorded in the study included birth weight, gestational age, gender, mode of delivery, 1- and 5-minute Apgar scores, history of maternal addiction and hypertension, delivery room resuscitation, surfactant therapy, duration of oxygen therapy and mechanical ventilation, oxygen and carbon dioxide levels of blood, mode of mechanical ventilation, times of packed cell transfusion, need for phototherapy, fresh frozen plasma, granulocyte colony stimulating factors, total parenteral nutrition, history of necrotizing enterocolitis (NEC), and patent ductus arteriosus.

Data analysis was performed in SPSS (version 20). Descriptive, Chi-square, and Fisher's exact tests were used for the qualitative data. For the quantitative data with abnormal distribution, Mann-Whitney U test was used. Statistical analysis was performed considering 95% confidence interval and p-value less than 0.05.

Results

Our study was performed on 154 preterm neonates with respiratory distress syndrome and prematurity as the most common reasons for admission in 66% of the cases. The study

population consisted of 59 (38.3%) females with the mean gestational age of 28.53±1.82 weeks (range: 25-32 weeks) and mean birth weight of 1049.66±236.94 g (range: 550-1450 g). There were also 95 (61.7%) males with the mean gestational age of 28.80±1.82 weeks (range: 23-32 weeks) and mean birth weight of 1155.47±240.982 g.

Mean gestational age of all newborns was 28.69±1.82 weeks (range: 23-32 weeks), and mean birth weight was 1114.94±240.982 g (range: 550-1500 g). The ROP was detected in 76 (49.4%) patients, 55.26%, 34.2%, and 10.53% of whom had ROP stages 1, 2, and 3, respectively. Stages 4 and 5 were not seen in our patients. The lowest gestational age of the patients was 23 weeks with the highest ROP incidence rate (100%), but most of the patients that were at 28 weeks of gestation had the ROP incidence rate of 50%. Our study revealed significant differences between the different groups of gestational age in terms of ROP (P=0.001). In this regard, with the reduction of the gestational age, the likelihood of ROP was increased.

In our study population, the minimum birth weight was 500-600 g with the ROP incidence rate of 100%, but the most frequent birth weight of patients was 800-899 g with the ROP rate of 50%. Similar to gestational age, there was a significant difference between the groups of different birth weights regarding the rate of ROP (P=0.001). Out of 59 females and 95 males, 34 (57.63%) and 42 (44.21%) cases had ROP, respectively, without any statistically significant differences (P=0.073). The Spearman's rank correlation coefficient demonstrated a weak correlation between the gender of the patients and the incidence of ROP without statistically significant differences (P=0.053).

As shown in Table 1, there were no statistically significant differences between the patients with and without ROP regarding the mode of delivery (P=0.571), places of delivery (i.e., inborn or out born; P=0.282), history of maternal addiction (P=0.745), maternal hypertension (P=0.112), surfactant therapy (P=0.301), intrauterine growth retardation (P=0.256), history of NEC (P=0.512),

Table 1. Relationship of demographic and clinical data with retinopathy of prematurity

variables	ROP +	ROP-	P-value
Mode of delivery			
C/S (87%)	49.3%	50.7%	0.570
NVD (13%)	50%	50%	
Place of delivery			
Inborn (92.9%)	50.3%	49.7%	0.282
Out born (7.1%)	36.4%	63.6%	
Maternal addiction (1.3%)	50%	50%	0.745
Without addiction (98.7%)	49.3%	50.7%	
Maternal hypertension (14.3%)	63.6%	36.4%	0.112
Normal blood pressure (85.7%)	47%	53%	
Delivery room resuscitation (22.1%)	67.6%	32.4%	0.013
No resuscitation (77.9%)	44.2%	55.8%	
Phototherapy (81.8%)	54%	46%	0.012
No phototherapy (18.2%)	28.6%	71.4%	
Surfactant therapy (59.1%)	51.6%	48.4%	0.301
No surfactant therapy (40.9%)	46%	54%	
FFP (14.9%)	60.9%	39.1%	0.166
No FFP (85.1%)	47.3%	52.7%	
GCSF (0.65%)	-	100%	0.494
No GCSF (99.35%)	49%	51%	
IUGR (13%)	40%	60%	0.256
AGA (87%)	50.7%	49.3%	
PDA (54.5%)	53.6%	46.4%	0.162
No PDA (45.5%)	44.3%	55.7%	
TPN (98.1%)	49.7%	50.3%	0.51
No TPN (1.9%)	33.3%	66.7%	
NEC (3.2%)	40%	60%	0.512
No NEC (96.8%)	49.7%	50,3%	
IVH (17.5%)	63%	37%	0.089
No IVH (82.5%)	46.5%	53.5%	
Packed cell transfusion (78.6%)	(table 5)	(table 5)	<0.001
No packed cell transfusion (21.4%)	9.1%	90.9%	

PDA: patent ductus arteriosus, TPN: total parenteral nutrition, NEC: necrotizing enterocolitis, IVH: intraventricular hemorrhage,

Figure 1. Relationship between the duration of oxygen therapy and prevalence of retinopathy of prematurity

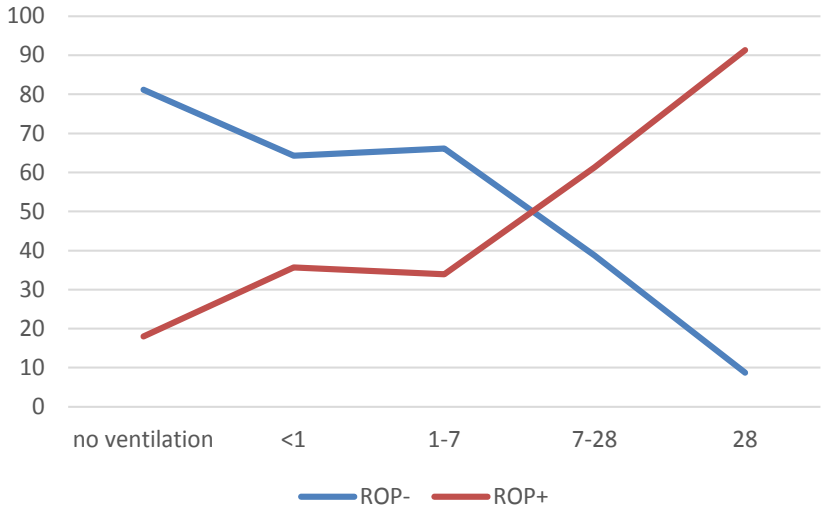

Figure 2. Relationship between duration of mechanical ventilation and prevalence of retinopathy of prematurity

and IVH (P=0.089). However, the history of phototherapy (P=0.01) and delivery room resuscitation (P=0.013) had significant differences between the two groups.

One of the most important reasons for the incidence of ROP in preterm newborns is oxygen therapy or mechanical ventilation. In this research, we analyzed the correlation between the duration of these two factors with ROP. Our results showed that the most periods of oxygen therapy in our patients was 1-10 days with an incidence rates of ROP in22.2% , but in cases with oxygen therapy between 11-20 days, ROP was detected in 50%, Furthermore, an oxygen therapy duration of > 21 days was associated with a higher rate of ROP, and an oxygen therapy duration of > 51 days was accompanied with 100% ROP incidence. Figure 1 illustrates the relationship between oxygen therapy duration and the incidence of ROP.

Most of the patients (40.3%) had the mechanical ventilation duration of 1-7 days with the ROP rate of 33.9%. Our research showed that the mechanical ventilation duration of > 7 days was accompanied by a higher rate of ROP, and that this factor had a significant effect on the incidence of disease (P=0.001). Figure 2 shows the relationship of mechanical ventilation duration with the incidence of ROP.

The usual modes of mechanical ventilation that

are used in our NICU are invasive (endotracheal) and noninvasive (nasal) forms. In this study, we analyzed the rate of ROP in our patients based on the mode of mechanical ventilation. In the eligible cases, 34.4% of the patients received both forms of mechanical ventilation (i.e., invasive and noninvasive forms). The patients treated with both types of mechanical ventilation at different times of NICU stay had the highest rate of ROP. There was a statistically significant difference in ROP incidence in our patients based on the mode of mechanical ventilation (P=0.002).One of the most common problems of premature and sick neonates in NICUs is anemia; accordingly, the rate of packed cell transfusion is high in these patients. Out of 154 neonates, 121 (78.6%) cases had the history of packed cell transfusion, and the times of packed cell transfusion had a significant effect on the incidence of ROP (P=0.001)

The Apgar score as an early indicator of oxygen therapy from the first minutes of life and hypoxic ischemic encephalopathy were evaluated in our study. Most of the patients (31.8%) had an Apgar score of 7 with the ROP rate of 44.4%. In patients with the Apgar score of ≤ 6, the ROP rate was higher. Our analysis revealed that there was a significant difference in the Apgar score of the first minute (P=0.032) unlike the 5th minute Apgar score (P=0.161).

In the analysis of arterial blood gas and the minimum and maximum levels of PH, $PaCO_2$, and PO_2, there was no significant association between different levels of arterial blood gas markers and ROP. The underlying disease did not have any effects on the incidence of ROP (P=0.486)

Discussion

Impaired growth in the vascular systems in the retina among preterm neonates causes ROP with some sequels and visual impairments in these patients, such as retinal detachment, amblyopia, myopia, and other visual problems (11, 30). Almost all preterm newborns with the history of NICU admission are at the risk of this disease and must be screened or treated (2, 31). Despite the enhancement of the survival rate of preterm neonates in NICUs in all parts of the world, the morbidities of prematurity are increasing. The ROP is one of the most important problems in these patients (32).

The multifactorial nature of ROP has deterred the prevention of this disease despite the professional care of preterm infants in NICUs (28, 33). In this research, we evaluated many risk factors for ROP in our patients and found that 50% of the preterm neonates with a gestational age of < 32 weeks had ROP with different stages, and stage 1 was the most prevalent state of the disease.

As recommended in many guidelines, the appropriate time of the first examination for screening and diagnosis of ROP is based on the postmenstrual age (PMA, i.e., gestational age plus postnatal age) of 31 weeks rather than postnatal age alone (27, 33). Many prospective studies revealed that the newborns with the gestational age of 22-25 weeks did not have stage 3 or more in the postmenstrual age lower than 31 weeks. However, in our practice in Mahdieh Hospital, regardless of PMA, the first ophthalmologic examination of the patients was performed in the 4^{th} weeks of life by an expert ophthalmologist. Our results showed that this time was appropriate for the early diagnosis and follow-up of the patients (34).

In line with our results, in a study performed by Rasoulinejad et al. in 2016 (10), the prevalence of ROP was reported as 45% in 306 neonates in Babol, Iran. The most common risk factors were introduced as prematurity, low birth weight, and oxygen therapy more than 5 days. However, in our research, oxygen therapy more than 21 days had a statistically significant effect on the rate of ROP.

In another mehta -analysis conducted in Iran on 1,053 cases from 50 studies, the prevalence of ROP was different from 6% in 2001 to 24.1% in 2016 with this justification that the increase in the survival of more preterm neonates in recent years has enhanced the prevalence of the disease (35). We have no information on the prevalence of ROP in our ward, but with regard to the enhancement of the survival of premature infants, ROP incidence has increased.

In a similar study by Alajbegovic-Halimic (36) in 2015, the rate of ROP was 48.8%. In the mentioned study, 6.2% of the cases were severe forms that required treatment, and 93.8% of them needed spontaneous resolution. In the mentioned study, the patients with younger gestational age, lower birth weight, and lower 1- and 5-min Apgar scores had the most severe form of disease. In our research, 10.26% of the detected ROP cases were in stage 3 as the most severe form of the disease.

Mode of delivery has been reported to affect the incidence of ROP. In this regard, in a study investigating the mode of delivery and ROP (37), Manzoni (2007) observed the severe form of ROP in neonates delivered through vaginal delivery.

Therefore, the authors recommended close ophthalmological surveillance in preterm infants born through normal vaginal delivery with a birth weight lower than 1,000 g. However, in our study, 87% of the cases were delivered through caesarian section (C/S), and there was no difference in the rate of ROP between the C/S and normally delivered neonates (49.3 % vs. 50%).

As we mentioned previously, in 56%, 34.2%, and 10.26% of our cases, the disease was in stage 1, stage 2, and stage 3, respectively. We did not have any cases with stages 4 or 5 of ROP; however, this promising result may be due to the fact that most of the premature and sick neonates in our population have a high mortality rate before ophthalmologic examination and detection of the disease. Accordingly, the present study was performed on only 154 preterm newborns. It is probable that in another study with a larger sample size, more advanced forms of disease could be reported.

Oxygen and mechanical ventilation are known as the two main causes of disease in preterm neonates. In our research, the prolonged duration of these treatments was accompanied by a higher disease incidence. In this regard, more premature and sick newborns with long periods of respiratory care have a higher risk of exposure to other factors causing the disease.

Although the prolonged period of oxygen therapy is important, the precise duration of oxygen therapy that is accompanied by ROP is not clear yet. Therefore, more investigations are needed to determine the exact safe duration and concentration of oxygen therapy in preterm neonates (38). With regard to the influence of many genetic and environmental factors on the prevalence of disease, some researches have emphasized that the detection of some other mediators downstream of oxygen is necessary.

Packed cell transfusion with adult hemoglobin A of lower affinity to oxygen increases the risk of ROP in the preterm newborns (39). There are many studies having evaluated this effect, and their results have been variable. In a recent cohort study conducted on 120 neonates, the rate of ROP was reported to be higher in the patients with a history of transfusion during the 30 days of life. Some other researches have also emphasized the impact of packed cell transfusion during the first 7 days of life on the incidence of disease (40).

In our research, the time of transfusion had a significant effect on the disease (P=0.001). This result showed that in sick newborns with a repeated history of transfusion, more care is needed for the timely diagnosis and treatment of ROP. In this regard, the restricted policy of transfusion in preterm infants seems logical. Similar to our study in the research by Sabzehei in 2013, blood transfusion higher than 45 ml/kg had a significant effect on the incidence of ROP (37).

The limitations of our study were the small sample size and lack of prolonged and post-discharge follow-up for the better determination of the consequences and prognosis of patients. The strength of the study was the evaluation of multiple risk factors for ROP in our preterm neonates.

Conclusion

Our research revealed a high prevalence of ROP in our patients. Low gestational age and birth weight, delivery room resuscitation, prolonged oxygen therapy and mechanical ventilation, and repeated packed cell transfusion had statistically significant effects on the incidence of ROP. Despite the improvement in the care of preterm neonates in NICUs, the rate of ROP is high. Therefore, the neonates at the risk of the disease need to receive better care for disease prevention, regular planned screening, and treatment programs for timely diagnosis and treatment.

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Conflicts of interests

Authors indicated that there are no conflicts of interest.

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