ORIGINAL RESEARCH PAPER

Opthalmology

PREDICTIVE FACTORS FOR SPONTANEOUS REGRESSION OF RETINOPATHY OF PREMATURITY IN A TERTIARY CARE INSTITUTE IN CENTRAL INDIA

KEY WORDS: Retinopathy of prematurity, Spontaneous regression, birthweight, oxygenation

Dr Shaikh Naziya Md Rizwan MS Ophthalmology, Gandhi Medical College, Bhopal

Dr Aditi Dubey Assistant Professor, Ophthalmology, Gandhi Medical College, Bhopal

Dr. Kavita Kumar Head Of Department, Ophthalmology, Gandhi Medical College, Bhopal

Dr Preeti Waskel* MS Ophthalmology, Gandhi Medical College, Bhopal *Corresponding Author

ABSTRACT

Aim: The aim of this study is to identify the factors affecting spontaneous regression of Retinopathy of prematurity. **Methods and Material:** All the neonates with gestational age of <37 weeks and/or <2kgs birth weight were screened and demographic data and data regarding the risk factors were noted at the start of study from their birth cards and medical cards they carried with them and was noted in a proforma. In those neonates in whom the Retinopathy of Prematurity presented or progressed to type 1 ROP were treated. Rest of them were followed as per ICROP (2005) guidelines till complete vascularisation. Risk factors were compared between the two groups. The Statistical analysis was performed by SPSS 23.0 version. **Results:** In the study 426 neonates were screened of them 183 eyes of 94 neonates had ROP. Sixty three neonates had spontaneous regression and 31 were treated as per ETROP guidelines. Mean gestational age in spontaneous regression group was 32.24±2.14 weeks, and that of treatment group was 29.9 ±2.44 weeks. This difference was statistically significant (P<0.001). Mean birth weight in spontaneous regression group was 1449.84±288 grams, and that of treatment group was 1309.93 ±291.06 grams. This difference was statistically significant (P=0.023). Oxygenation and NICU hospitalisation <1 week, anemia and blood transfusion, lesser weight gain in the initial 6 weeks were found to significantly affect spontaneous regression of ROP (P<0.005). Higher gestational age, Oxygenation and NICU hospitalisation <1week were found to independently influence spontaneous regression of ROP. **Conclusions:** The gestational age of infant is an important predicting factor in spontaneous regression of ROP. Longer duration of oxygenation and NICU hospitalisation are important factors affecting spontaneous regression of ROP inversely.

INTRODUCTION

The incidence of premature births all over the world in 2014 was as high as 15 million, a rate that has been rising since the past 20 years[1]. It is estimated that approximately one in ten new-borns is born prematurely worldwide, more than 1 million children die each year from complications of premature birth, and those who survive face a lifetime of disabilities, including learning disabilities, hearing disabilities, and visual impairments[2]. Retinopathy of Prematurity is one of such problems in preterm infants which is potentially vision threatening if not identified and treated on time. With the advances in perinatal care and increased survival of preterm neonates in developing countries there has been a rise in the cases which has led to the emergence of third surge[3]. India is one such developing country facing the third epidemic with the incidence of ROP being as high as 38% to 47% noted in different regions of India[4].

There have been many studies for evaluation of risk factors of ROP in which birth Weight, gestational age (GA), supplemental oxygen, prolonged mechanical ventilation, APGAR score, pulmonary complications, anaemia, intraventricular haemorrhage (IVH), necrotizing enterocolitis, sepsis have been found to increase ROP incidence[(8-10)]. However in the current literature, there are few studies for the factor affecting the spontaneous regression of ROP.

In most cases spontaneous regression of ROP occurs without serious sequelae in eyes with earlier stages 1, 2 and early stage 3, while in higher stages blindness or other sequelae such as retinal detachment and distortion of posterior retina may cause serious visual impairment and even lead to blindness[11]. Identifying the risk factors involved in the progression of ROP and a better understanding of their etiology and natural course of regression can help in the development of effective and efficient screening and monitoring strategies for detection and treatment of ROP at correct time in a resource limited setting as well as low reach areas.

Also knowing these factors will help us to identify the stages which has more propensity for spontaneous regression so that over treatment and treatment related complications are avoided.

Methodology:

After approval of the study protocol by the Institutional Ethics Committee, the study was initiated. A prospective observational study was conducted over a duration of 1.5 years from December, 2019 to May, 2021 in a tertiary care institute in central India.All infants presenting to ROP Clinic of our tertiary care centre with gestational age of <37 weeks and/or <2kgs birth weight were screened as well as the patients referred from peripheral hospitals were included in the study. Parents were explained about the procedure and proper consent was taken. Demographic data of all the infants were noted and recorded in a preformed proforma. Data regarding the risk factors like duration of NICU hospitalisation and oxygenation and mechanical ventilation, apnoea, asphyxia, PDA, sepsis (culture positive / CRP positive), anaemia Hb <110mg/dl, blood transfusion and number of units of blood transfused, hyperbilirubinemia (bilirubin>15mg/dl), phototherapy were noted at the start of study from their birth cards and medical cards they carried with them. Maternal risk factors like, PIH, Preeclampsia and eclampsia, Premature Rupture of membrane, Singleton or multiple pregnancy, Exclusive Breast feeding. All neonates with anterior segment pathology or posterior segment pathology other than ROP and those with irregular follow up during the screening period or those who did not survive the maximal screening ROP period were excluded. Posterior segment examination was performed using a binocular indirect ophthalmoscope, a paediatric lid speculum, and a 28-

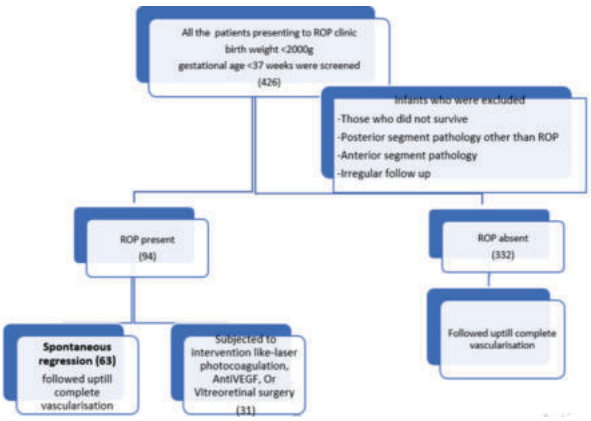
diopter lens after instilling topical anaesthetic eyedrop proparacaine 0.5%. A scleral indenter was used to examine the retinal periphery.The zone of vascularization (from I to III), presence or absence of plus or pre plus disease, and the stage of ROP (stages 1–5) were evaluated as per International Classification of ROP-2. Neonates in whom Retinopathy of Prematurity either presented or progressed to type 1 ROP were treated. Rest of them were followed as per ETROP guidelines till complete vascularisation. While statistical analysis for factors for spontaneous regression, the two eyes cannot be considered as separate entity so the eyes with more severe disease was considered for analysis.The highest stage was considered for statistical evaluation which occurred during the entire course of regression.

Statistical analysis:

The Statistical analysis was performed by SPSS 23.0 version. Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean ± SD (analysed using independent t test) if they followed normal distribution and were described as Median (IQR) if they followed non normal distribution. Categorical variables were described by taking percentages (analysed using Chi Square test; Subgroup analysis was based on Adjusted Standardized Residuals). Differences between 3 groups in continuous variables was analysed using One Way ANOVA test and further Subgroup analysis of the significant variables was done using a Post Hoc test (Tukey's test). Univariable analysis for factors affecting spontaneous regression was done using the tests mentioned above. Multivariable analysis for factors affecting spontaneous regression was done using Binary Logistic Regression on the factors which were significant on Univariable analysis. Variables with p value <0.05 was considered as statistically significant.Figure 1:Flowchart of study

RESULTS:

In the present study a total of 426 neonates were screened, and out of them 94 neonates had ROP. From those who had ROP 63 had spontaneous regression while 31 had disease which needed intervention. In the study population mean gestational age of neonates undergoing spontaneous regression was 32.24 ± 2.14weeks, which is significantly higher than those who required treatment, mean GA was 29.9 ± 2.44weeks**(P=<0.001)**. Thus, higher gestational age is a predictive factor for spontaneous regression.



The mean Birth weight in spontaneous regression group was 1449.84 ± 228g which is significantly higher than in those who required treatment, 1309.93 ± 291.06g(**P=0.023**). So, the higher birth weight is a positive predictive factor for spontaneous regression of ROP(Table 1).

In univariate analysis lesser duration of NICU hospitalisation (<1 week) and Oxygenation (<1 week) are predictive of spontaneous regression of ROP. Whereas anemia and Blood transfusion, lesser weight gain in the initial 6 weeks led to more severe form of ROP or affected the spontaneous regression of ROP negatively.(Table 2)

On multivariate analysis higher gestational age and lesser duration of NICU stay and oxygenation were found to be independently responsible for spontaneous regression of ROP.(Table 3)

Demographic characters			Treatment Received (N=31)	Spontaneous Regression (N=63)	P value
Gestational Age		Mean ± SD	29.9 ± 2.44	32.24 ± 2.14	**<0.001**
Gender	Males	Number (Percentage)	20 (64.5)	37 (58.7)	0.589
	Females		11 (35.5)	26 (41.3)	
Birth Weight		Mean ± SD	1309.93 ± 291.06	1449.84 ± 228	**0.023**
Residence	Urban	Number (Percentage)	17(54.8)	35(55.55)	0.9475
	Rural		14(45.16)	28(44.44)	
Maternal nutrition (anaemia)			23(74.2)	48(76.2)	0.8323

Table 1: Demographic characteristics of neonates having ROP.

Factors		Treatment Received (N=31)	Spontaneous Regression (N=63)	P value
		Number (Percentage)	Number (Percentage)	
Mode of Delivery	NVD	29 (93.5)	55 (87.3)	0.356
	LSCS	2 (6.5)	8 (12.7)	
NICU Hospitalization	< 1 week	11 (35.5)	49 (77.8)	**<0.001**
	>1 week	20 (64.5)	14 (22.2)	
Oxygenation	<1 week	9 (29)	36 (57.1)	**0.01**
	> 1 week	22 (71)	27 (42.9)	
RDS		27 (87.1)	46 (73)	0.187
Asphyxia		5 (16.1)	3 (4.8)	0.11
Sepsis		22 (71)	40 (63.5)	0.472
PDA		6 (19.4)	5 (7.9)	0.105
Anemia (Hb<110gm/L)		15 (48.4)	13 (20.6)	**0.006**
H/o blood Transfusion		14 (45.2)	11 (17.5)	**0.004**
Raised bilirubin		19 (61.3)	31 (49.2)	0.27
		Mean ± SD	Mean ± SD	0.276
Intraretinal Haemorrhage		6 (19.4)	7 (11.1)	7 (11.1)
Average Weight Gain per week in initial 6 weeks		432.52 ± 10.79	441.16 ± 12.76	**0.001**
Multiple Pregnancy		7 (22.6)	21 (33.3)	0.284
PROM		1 (3.2)	2 (3.2)	1
H/o PIH		4 (12.9)	2 (3.2)	0.09
Eclampsia		4 (12.9)	3 (4.8)	0.213
Exclusive Breast Feeding		17 (54.8)	45 (71.4)	0.111

Table 2: Univariate analysis of Neonatal and maternal factors in spontaneous regression of ROP

Factors	P value	Odds Ratio
Gestational Age	0.002	1.585
Duration of NICU <1 week	0.016	4.889
History of oxygenation <1 week	0.032	4.874

Table 3: Multivariate analysis for factors in Spontaneous Regression of ROP

DISCUSSION:

ROP is a disease with varied outcomes. The spectrum of sequelae ranges from spontaneous regression of the early stages to progression to irreversible and difficult to treat retinal detachment cases. It is important to identify the disease in early stages and associated factors so that appropriate stage specific treatment can be done to prevent its progression and to follow up patients till complete vascularisation

In the present study higher gestational age and birth weight are positive predictive factor for spontaneous regression of ROP. This is consistent with the finding of the **CRYO-ROP (1993)**[12] A Multicenter Trial which included 4099 infants. Lower BW and younger GA were associated strongly with

developing more severe "threshold" ROP. Each single week increase in GA decreased the odds of reaching threshold disease by 19%.

An important part of the nutritional support to the fetus occurs in the last trimester, and when an infant is exposed to extrauterine environment prematurely, maternal support of insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein 3 (IGF-1BP3) are lost and it results in delayed physiologic retinal vascular development[13]. Lower birth weight is an indicator of immaturity as well impaired antenatal weight gain and growth restriction. Factors that can cause an increased risk of development of ROP in low birth weight babies are chronic uterine hypoxia, abnormal growth factor levels, nutrient restriction, and antioxidant deficiency[14].Hence, lower gestational age and birth weight affects spontaneous regression of ROP negatively.

Lesser duration of NICU hospitalization is positive predictive factor for spontaneous regression of ROP. Which is consistent with the studies by **Rui-Hong Ju et.al**[15] and **Awadein AR, et al.**[16] In the study conducted by **Rui-Hong Ju et.al (2013)**[15]**,** it was found that length of NICU hospitalisation <10 days is one of the positive predictive factors for spontaneous regression of ROP.

Awadein AR, et al.(2017)[16] in his retrospective cohort study to evaluate the risks for retinopathy of prematurity found that longer duration of hospitalisation is responsible for development and progression of ROP. But at times NICU hospitalisation may be indicative of severe illness burden and other comorbidities, which may act as confounders for its association with severe ROP requiring treatment.

Oxygen supplementation of lesser duration (<7days) is positive predictive factor for spontaneous regression of ROP.This is comparable to study carried out by **Rui-Hong Ju et.al(2013)**[15] **and, Tarah T Colaizy et al. (2017)**[17]**.** In the retrospective study carried out by **Rui-Hong Ju et.al (2013)**[18], oxygen therapy was identified as a possible risk factor for progression of ROP. **Tarah T Colaizy et al. (2017)**[17] in a retrospective study for comparing the progression of ROP before and after institution of an oxygen therapy protocol. suggested that appropriate oxygen therapy may play a role in inhibiting the progression of stage 2 ROP.

In the present study anemia was found to negatively affect spontaneous regression of ROP. This result is comparable to findings of **Wang et.al (2021)**[18]. In the study conducted by **Wang et.al (2021)**[18], 5-year retrospective study to evaluate clinical features of spontaneous regression of retinopathy of prematurity in China. Two hundred thirty-seven eyes of 237 paediatric patients were included. Anaemia was identified as independent risk factors for delayed regression by survival analysis.

Because of insufficient erythropoiesis due to inadequate production of erythropoietin, decreased hemoglobin concentration after birth is particularly found among preterm infants which is termed as the 'anaemia of prematurity'.

In the present study blood transfusion was found to negatively affect spontaneous regression of ROP. This result is comparable to the studies by **Bejeh Mir KP et al**[19] **and Cota F, et al.(2012)**[20].

RBC transfusion influences ROP mainly in two ways. First, RBC transfusion increases iron intake, thereby increasing the level of its oxidation product. Secondly, unlike fetal hemoglobin (HbF), adult hemoglobin (HbA) has a lower affinity for oxygen, thereby shifting the oxygen hemoglobin dissociation curve to the right and unloading more oxygen to the developing retina after the transfusion of adult blood products[21].

Moreover, blood transfusions, recombinant erythropoietin to treat or prevent anemia, and anemia themselves are ROP risk factors. So it is important to look for haemoglobin in ROP cases and treat accordingly so that risk of progression and chances of spontaneous regression is increased.

Postnatal weight gain may be indicative of overall health in the neonate. In the present study the mean weight gain during the initial 6 weeks was found to be significantly higher in the spontaneous regression group. These finding is comparable to the findings of **Yingxiang Li et al.(2019)**[22], **AnaMaria Solans P´erez de Larraya et al (2019)**[23].

The scientific rationale is that slow weight gain is a measure for a slower than expected rise in serum insulin–like growth factor-1 (IGF-1), which results in insufficient activation of retinal vascular endothelial growth factor by IGF-1 and poor retinal vascular growth early in postnatal life[23].

Conclusion: Retinopathy of prematurity is a retinal vascular disease, with varied outcomes and has a clinically identifiable disease onset. Most of the disease regresses spontaneously without any intervention. Regular screening, proper follow up and identifying the disease when it has the propensity to progress and appropriate intervention at right time is the key factor to prevent its sight threatening complication. Moreover, identifying the factors which may affect spontaneous regression is important to identify the natural course and predict spontaneous regression in the predisposed infants.

Higher birth weight and higher gestational age at birth, lesser duration of NICU stay and oxygenation, relatively high average weight gain in the initial 6 weeks were significantly associated with spontaneous regression of ROP. Neonatal anemia and blood transfusion were significantly associated with less spontaneous regression

Though birth weight and less gestational age are factors which are difficult to modify, weight gain in the postnatal period, irrational oxygen supplementation and NICU hospitalisation, anemia and blood transfusion must be avoided to the extent possible to prevent ROP from taking a detrimental route to 'type 1 ROP' which requires intervention. Moreover, treatment of ROP is associated with its own set of complications.

The weakness of this study is that the sample size was less and high dropout rate was seen in this duration due to COVID-19 pandemic and restriction. In the present study oxygen exposure was measured in terms of duration of oxygenation. However, quantification with respect to oxygen concentration and oxygen saturation (SpO_2) was not done. The newer classification of ROP (ICROP 3) could not be implemented in this study since the study was started earlier.

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