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Study of factors affecting the duration of spontaneous regression of retinopathy of prematurity

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ABSTRACT

Aim: The aim of this study was to identify the factors influencing the duration of spontaneous regression of Retinopathy of Prematurity.

Materials and Methods: A prospective observational study was conducted over a duration of 1.5 years from December, 2019 to May, 2021. All the infants presenting with ROP or developed any stage later were considered for the study and were followed up as per International Classification of Retinopathy Guidelines (ICROP), 2005 guidelines till compete vascularisation. Data regarding the birth history and maternal factors were noted. In those neonates in whom the Retinopathy of Prematurity presented or progressed to type 1 ROP were treated and the rest were followed up till complete vascularisation and duration noted. Risk factors were compared in neonates undergoing spontaneous regression within 45 weeks PMA and those taking longer than 45 weeks. The Statistical analysis was performed by SPSS 23.0 version.

Results: Mean gestational age in neonates undergoing earlier spontaneous regression (<45 weeks) was 31.86±2.02 months, and that of delayed spontaneous regression group was 33±2.24 months. Mean birth weight in earlier spontaneous regression group was 1537.14±202.02 grams, and that delayed spontaneous regression group was 1406.19±229.88 grams. Mean duration of complete regression of ROP is 44.9 weeks postmenstrual age. Higher birth weight and Hyperbilirubinemia was found to significantly cause the regression of ROP within 45 weeks (P=0.021).

Conclusions: Higher birth weight and Hyperbilirubinemia was found to cause earlier regression of ROP and hence could be a possible protective factor in the pathogenesis of ROP.

1. Introduction

Retinopathy of prematurity (ROP) is a condition characterized by the development of abnormal vessels in retina secondary to an incomplete vascularization of the retinal tissue due to hyperoxia causing downregulation of VEGF and death of endothelial cells. This mechanism suggests that VEGF has a vital role for the endothelium. Following the closure of growing vessels, the retinal tissue in development becomes ischemic and hypoxic. This process upregulates VEGF leading to neovascularization.[1–3] Not just hyperoxia but there are myriad of other factors which have a role in the pathogenesis of ROP.

Birth Weight, Gestational age (GA), supplemental oxygen, prolonged mechanical ventilation, APGAR score, pulmonary complications, anaemia, intraventricular haemorrhage (IVH), necrotizing enterocolitis, sepsis are some of the risk factors influencing ROP development.[4–10]

In premature babies knowing the course and duration of regression helps in strategizing the review timings. Repka et al.[11] reported 90% of ROP cases started involuting before 44 weeks of postmenstrual age. In the literature there are

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very few studies evaluating the factors affecting the duration of regression. The purpose of this study is to evaluate the time course of regression of ROP and also evaluate the factors which may delay regression.

2. Materials and Methods

All the infants presenting to retina clinic at our tertiary care hospital were screened for ROP and those infants who presented with ROP or developed any stage later were considered for the study and were followed up as per International Classification of Retinopathy Guidelines (ICROP), 2005 guidelines till compete vascularisation. Parents were explained about the procedure and proper consent was taken. 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. 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. The neonatal and maternal factors considered for study were: Gestational age, Postmenstrual age, Birth weight, Residence, Maternal nutrition (assessed by medical records and blood reports; Hb levels), Duration of NICU hospitalisation, Duration of 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, Average weight gain during the first 6 weeks calculated from the growth cards of neonates. And also Maternal risk factors like PIH, Preeclampsia and eclampsia, Premature Rupture of membrane, Singleton or multiple pregnancy, Exclusive Breast feeding. 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(2005). The neonates who were followed up till complete vascularisation was completed and were divided into two groups based on the duration required for complete spontaneous regression into those who regressed within 45 weeks of postmenstrual age and those who needed more than 45 weeks. 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.

2.1. 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.

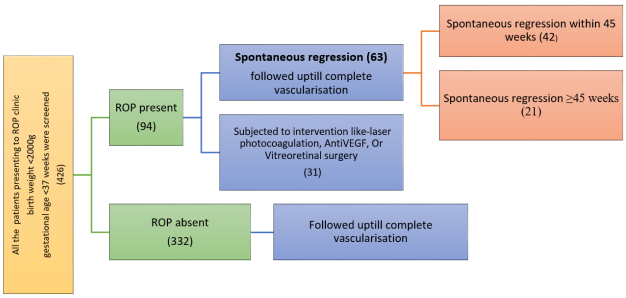

Chart 1: Flow chart of this study

3. Results

In the present study a total 426 infants were screened, of them 94 were diagnosed with ROP. Out of these 63 regressed spontaneously whereas 31 required intervention. In those patients undergoing spontaneous regression, earlier spontaneous regression (<45 weeks PMA) was noted in 42 infants and delayed spontaneous regression ≥45 weeks PMA) was noted in 21 infants.

Mean gestational age in neonates undergoing earlier spontaneous regression (<45 weeks PMA) was 31.86± 2.02 months, and that of delayed spontaneous regression group was 33±2.24 months. Mean birth weight in earlier spontaneous regression group was 1537.14±202.02 grams, and that delayed spontaneous regression group was 1406.19±229.88 grams, which is significantly lower as compared to earlier regression group. In the present study the mean PMA of onset of ROP was 36.6 weeks and that of complete regression was 44.9 weeks.

In the univariate analysis for factors leading to delayed regression, raised bilirubin was present in 59.2% of those

who had early regression (within 45 weeks) which is significantly higher as compared to those who regressed later(>45 weeks) (P =0.021).

Among all cases detected with ROP the rate of spontaneous regression of ROP was 92.1% in stage 1, 70.5% in stage 2 and 33.33% in stage 3.

Whereas zone wise rate of spontaneous regression is 93.33% in zone **I** and 73.6% in zone **II** and 30.4% in zone **III**. Thus, with the increasing severity of disease the spontaneous regression rate decreases.

4. 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. In the present study the mean PMA of onset of ROP was 36.6 weeks and that of complete regression was 45.9 weeks which is comparable to that of Repka et al.[11] in which mean time of onset of regression was 38.6 weeks 90% of the ROP regressed by 45 weeks. While in the study by Wang et al. (2021)[12] median time for complete regression was 49.0 weeks which is higher as compared to present study. This difference could be due to varying course of ROP in different ethnicity and race and different follow up criteria followed.

Mean duration of spontaneous regression in the current study is 8.34 weeks which is comparable to that given by the study by Wang et al (2021)[12] in which mean duration of regression was 8.5 weeks and Rui-Hong Ju et al[13] (2013) in which the mean duration of spontaneous regression was 5.65±3.14 weeks.

Ying-Qin Ni et al.[14] (2014) in his retrospective case series for the evaluation of risk factors associated with delayed involution, CPAP, and anemia were predictive risk factors for delayed involution of ROP. In the study conducted by Ana Maria Solans Perez de Larraya et al.[15] (2019) for the evaluation of factors associated with the speed of retinal vascularisation, intubation days, degree 3 of bronchopulmonary dysplasia and weight gain at 4-6 weeks of gestational age were found significant. In the present study, higher birth weight and hyperbilirubinemia was found to be associated with early regression of ROP.

Birth weight was also found significant in the study conducted by Gu MH et al[16] and Zong Hua et al.[17] Gu MH et al[16] in the study on 951 neonates with a birth weight between 700 and 2000g concluded that lower the birth weight higher is the incidence and progression of ROP. Zong Hua et al.[17] in the retrospective study to assess the relative effect of birth weight and gestational age on retinopathy of prematurity (ROP) using preterm twin pairs discordant for birth weight in a tertiary neonatal intensive care unit in China. Birth weight was significantly associated with the occurrence and progression of ROP.

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.[18]

Elevated bilirubin can be harmful, but bilirubin has been shown to be an antioxidant in vitro. Thus, to study the fact that bilirubin might be protective against ROP has caught the fancy of many investigators. and there have been inconsistent results. For the evaluation of possible protective effect of hyperbilirubinemia study Shigeharu Hosono et al. (2002)[19] conducted a study based on assessment of 76 infants born at 24 and 25 weeks' gestation. The study concluded that there is no distinct protective effect of bilirubin on the development of severe ROP. Joshua D Milner et al.(2003)[20] in his study to analyse whether elevated peak bilirubin protects from ROP in very low birthweight infants. Risk for ROP stages III and IV was measured as a function of increasing peak bilirubin levels in VLBW infants admitted to the neonatal ICU. It concluded that Elevated peak bilirubin does not protect from and may be a risk for ROP in VLBW infants. In a retrospective case control study conducted by Joanna S. Kao et al (2011)[21] for analysing the association of serum bilirubin level and breast milk feeding with retinopathy of prematurity (ROP) in preterm infants in which (66 infants with ROP) were matched with controls (66 infants without ROP). Higher serum bilirubin levels was found to be favourable for spontaneous regression of ROP and decreasing the risk of ROP. (OR=0.82 per 1-mg/dl change in bilirubin (P=0.06).

The present study showed spontaneous regression of 93.33% in zone **III** and 73.6% in zone **II** and 30.4% in zone **I** had spontaneous regression whereas 92.1% in stage 1, 70.5% stage 2 and 33.33% in stage 3 had spontaneous regression.

In the severe ROP the vascularization is delayed.[22,23] In the study conducted by Prost et al. (2003)[24] spontaneous regression was observed in 85% of children with stage 1, in 56% in stage 2 and in 25% in stage 3. While in zone III regression was noted in 95%, in zone II in 45% and in zone I in 6%.

And in retrospective hospital-based study conducted by Rui-Hong Ju et al[13] (2013), to evaluate the incidence of spontaneous regression of changes in the retina and vitreous in active stage of retinopathy of prematurity (ROP) the incidence of spontaneous regression of ROP with stage 1 was 86.7%, and with stage 2, stage 3 was 57.1%, 5.9%, respectively. With changes in zone **III**, spontaneous regression was detected 100%, 46.2% in zone **II** and 0% in zone **I**. The mean duration of ROP in spontaneous regression group was 5.65±3.14 weeks.

In the present study the incidence of spontaneous regression was comparable to previous 2 studies in zone

Table 1: Univariable analysis for factors affecting delayed Regression of ROP

Factors			Normal Regression (≤ 45 weeks) (N=42)	Delayed Regression (> 45 weeks) (N=21)	P value
Gestational Age		Mean ± SD	31.86 ± 2.02	33 ± 2.24	0.056
Gender	Males	Number (Percentage)	26 (61.9)	11 (52.4)	0.469
	Females		16 (38.1)	10 (47.6)	
Birth Weight		Mean ± SD	1537.14± 202.02	1406.19± 229.88	**0.025**
Average Weight Gain per week in initial 6 weeks			440.95 ± 10.65	441.57 ± 16.49	0.877
Mode of Delivery	NVD		38 (90.5)	17 (81)	0.423
	LSCS		4 (9.5)	4 (19)	
NICU	< 1 week		35 (83.3)	14 (66.7)	0.134
Hospitalization	>1 week		7 (16.7)	7 (33.3)	
Oxygenation	<1 week		26 (61.9)	10 (47.6)	0.28
	> 1 week		16 (38.1)	11 (52.4)	
RDS			32 (76.2)	14 (66.7)	0.422
Surfactant Given			0 (0)	0 (0)	NA
Asphyxia			2 (4.8)	1 (4.8)	1
Sepsis		Number (Percentage)	26 (61.9)	14 (66.7)	0.711
PDA			2 (4.8)	3 (14.3)	0.323
Anemia			9 (21.4)	4 (19)	1
H/o blood Transfusion			7 (16.7)	4 (19)	1
Raised bilirubin			25 (59.2)	6 (28.6)	**0.021**
Phototherapy			11 (26.2)	2 (9.5)	0.189
Multiple Pregnancy			13 (31)	8 (38.1)	0.571
PROM			1 (2.4)	1 (4.8)	1
H/o PIH			2 (4.8)	0 (0)	0.548
Eclampsia			2 (4.8)	1 (4.8)	1
Breast Feeding			31 (73.8)	14 (66.7)	0.554

Table 2: Spontaneous regression of ROP zone and stage wise

Stage	Zone III		Zone II		Zone I		Spontaneous regression
	Regressed	Required treatment	Regressed	Required treatment	Regressed	Required treatment	
Stage 1	8	0	20	2	7	1	92.1%
Stage 2	6	1	18	5	-	4	70.5%
Stage 3	-	-	4	5	-	3	33.33%
Stage 4	-	-	-	1	-	3	-
Stage 5	-	-	-	1	-	0	-
APROP	-	-	-	1	-	5	-
Spontaneous regression	93.33%		73.6%		30.4%		

Table 3: Comparison of incidence of spontaneous regression in different zones and stages

	Prost et al.	Rui-Hong Ju et al	Present study
Zone **I**	6%	0%	30.4%
Zone **II**	45%	46.2	73.6%
Zone **III**	95%	100%	93.33%
Stage 1	85%	86.7%	92.1%
Stage 2	56%	57.1%	70.5%
Stage 3	25%	5.9%	33.33%

III and stage 1. While in the present study there is higher incidence of spontaneous regression in more severe disease. This could be probably due to variation in the gender, Race, and geographic and socio-economic factors of different region and different criteria of defining ROP in different disease stages and interobserver variation in grading and staging of disease.

5. Conclusion

Regression of ROP in most cases occurred by 45 weeks, and hence a reduction in the frequency of follow ups can be done. Discontinuation of follow up is not indicated until complete vascularisation since higher stage and some factors like low birth weight in this study can cause delayed regression. Hyperbilirubinemia was found to cause earlier regression. Though the antioxidant effect of bilirubin might be attributed to the cause of early regression, due to lack of studies in the literature in this aspect and inconsistent results, conclusion cannot be drawn. More research is needed in this direction to evaluate the effects of Bilirubin level on ROP and for the evaluation of factors affecting the duration of regression of ROP.

6. Source of Funding

None.

7. Conflict of Interest

None.

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