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Original Research Article

RELATION OF RETINOPATHY OF PREMATURITY WITH CHANGE IN BIRTH WEIGHT DURING THE POSTNATAL PERIOD IN PREMATURE INFANTS IN A TERTIARY CARE HOSPITAL IN LAHORE

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Abstract: *This study assessed the relationship between Retinopathy of Prematurity (ROP) and post-natal weight gain in premature infants admitted to the Neonatal Intensive Care Unit (NICU). The observational study was conducted in the Department of Ophthalmology in collaboration with the Department of Pediatrics, the neonatal intensive care unit (NICU) at Sir Ganga Ram hospital in Lahore from September 2020 to August 2022. Data including gender, Birth Weight (BW), Gestational Age (GA), and post-natal complications(hypotension, packed red cell transfusion, intraventricular hemorrhage, necrotizing enterocolitis, and respiratory distress syndrome) of all the premature infants with gestational age less than 35 weeks, admitted in NICU was collected. All these premature infants underwent eye examination for the presence or absence of ROP, and weight was measured. In the second, fourth, and sixth weeks, their relative weight gain (RWG) was calculated. Infants with ROP had lower BW (P <0.001) and GA (P<0.001). More infants with severe ROP had body weight <1000g and post-natal complications than those without ROP. Moreover, RWG at the 2nd and 4th weeks was lower in infants with ROP than with no ROP infants. Based on the result, it can be concluded that the ROP was associated with low postnatal weight gain, birth weight, and gestational age.*

Keywords: Retinopathy of prematurity, birth weight, gestational age, post-natal weight gain

Introduction

Retinopathy of prematurity (ROP) accounts for 14% of child blindness cases (Taner et al., 2020). It is a visually threatening disorder in which the proliferation of retinal vessels occurs in preterm babies due to the immaturity of their retina, which makes them vulnerable to various injuries. Because of the continuous increase in cases of premature births daily in developing countries, ROP is now a topic of utmost attention. Despite the improvement in Neonatal Intensive Care Unit (NICU) facilities, it has become a significant public health problem. (2) The ROP incidence in developing and developed countries is varied. Mayd Riaz and co-workers 2019 conducted a cohort study at Hameed Latif Hospital Lahore, where all neonates with low birth weight and gestational age were examined. It showed that 28 % of those screened had developed ROP [3]. Retinopathy is related to prematurity and results due to abnormal retinal vessel growth. Retinal vascularization initiates in the 14th week of gestation and completes at the 40th week of gestation. Oxygen therapy given to preterm infants leads to hyperoxia, which decreases the production of vascular endothelial growth factor (VEGF) and halts the vascularization of the immature retina, leading to ischemia and hypoxia of retinal tissues, upregulating the VEGF, resulting neovascularization and abnormal retinal vessels. As there is an increase in survival rates among preterm babies due to the improved healthcare facilities, babies need more attention now as there is a greater risk of developing ROP.

The screening guidelines primarily use two risk factors, birth weight and gestational age. However, multiple studies have reported several other post-natal risk factors associated with ROP being a multifactorial disease, some of which can result in severe ROP like supplemental oxygen during neonatal care, prolonged mechanical ventilation, usage of surfactants, nutritional effects, extrauterine growth restriction, oxidative stress, pulmonary complications, anemia, low weight gain during neonatal period and sepsis.[4] Nutritional inadequacy in preterm infants is associated with a low level of IGF-1, which is correlated to severe ROP (Jensen et al., 2017). Studies have reported the association between ROP and postnatal weight gain (Li et al., 2019;

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Wongnophirun et al., 2020). Poor postnatal weight gain may be the predictor of advanced disease that requires laser treatment. Weight gain of less than 4.5 g/kg/ day in 2nd postnatal week is a predictor of ROP requiring treatment (Wongnophirun et al., 2020), weight gain of less than 380g or weight gain proportion of less than 42 % in 6th postnatal week may be the predictor of ROP stage 3. A weight gain (WG) proportion of less than 51% can also predict threshold ROP (Šarić et al., 2020). Variable results reflect regional nutritional and medical management differences and different population characteristics. This study aims to assess the association between ROP and post-natal weight gain and to determine the cut-off value for WG, which predicts the presence of retinopathy of prematurity in the Pakistani population. This will benefit the patient by not only preventing blindness but decreasing the burden on health resources. Different neonatologists and ophthalmologists will get help from our study to perform the cautious screening of preterm babies, accomplish an accurate diagnosis and prevent disease development. As per our knowledge, only limited data about ROP in Pakistan is available at the local level.

Methodology

The prospective study was conducted at the Ophthalmology department of Sir Ganga Ram Hospital, Lahore, in collaboration with the neonatal intensive care unit from September 2020 to August 2022. The study included premature infants of gestational age under 35 weeks and birth weight of fewer than 2000 gm who were admitted to NICU and then screened for retinopathy of prematurity. Infants having congenital abnormalities or whose data was missing were excluded. The study was conducted on a total of 240 infants. The parents were informed. The ethical board of the hospital approved the study. The birth weight, gestational age, surfactants given or not, type of oxygen therapy given, average saturation maintained during the stay at NICU, weight after 2 weeks' birth, and any complication during hospital stay were noted on proforma with the involvement of the pediatrics department. The child was examined and screened for the development of ROP either at the Ophthalmology department or NICU after 4 weeks of birth. One drop of tropicamide 0.5% topical eye drops combined with phenylephrine 1% eye drops were instilled in each eye after every 15 minutes 3 times for dilation of the pupil, and then fundoscopy was performed.

The retinal assessment used a binocular indirect ophthalmoscope and a 20-diopter lens (Volk, WA, USA) using a lid speculum and scleral indentor. The stage and zone of ROP, along with plus disease, if the present was documented. International Classification for Retinopathy of Prematurity was used for classifying ROP (Chiang et al., 2021). Based on ophthalmoscope assessment, ROP has been classified into 5 stages: A faint demarcation line is classified as stage 1, an elevated ridge is classified as stage 2, an extra-retinal fibrovascular tissue is classified as stage 3, and subtotal retinal detachment is classified as stage 4, while stage 5 is called when there is a total retinal detachment. If significant vascular dilation and tortuosity are present, it is labeled as plus disease and may present at any stage, indicating increased blood flow through the retina. The intervention was done in the presence of any ROP with plus disease in zone 1, stage 2 with plus disease, and stage 3 ROP in zone I or II. Laser treatment was done per standards (Emami et al., 2019).

The ROP patients not requiring any treatment were called after every 2 weeks till the gestational age of 40 weeks or the complete vascularization of the retina, whichever occurred first. The ROP patients requiring any intervention were followed weekly till the regression of vessels, then 2 to 4 weekly until no active ROP existed. During each visit, fundus evaluation was done, and the baby's weight was noted. The child who failed to gain weight was communicated to the pediatrics department and was referred for management. Data including gender, birth weight, gestational age, post-natal complications (packed red cell transfusion, hypotension, sepsis, Intraventricular Hemorrhage (IVH), respiratory distress syndrome (RDS) requiring surfactant and Necrotizing enterocolitis (NEC) was reviewed. In the second, fourth, and sixth weeks, relative weight gain (RWG) was calculated. The formula for calculating RWG was: RWG (g/kg/day) = [body weight (g)—birthweight (g)] / birthweight (kg) / postnatal age (d)

SPSS version 22 was used for data analysis. Results were presented as frequency and median. Mann–Whitney U-test was used for the analysis of continuous variables. $\chi 2$ or Fisher Exact test was used to compare the categorical variables. Risk factors were identified using univariate logistic regression analysis. The cut-off value of relative weight gain and gestational age for predicting ROP requiring treatment were determined using the receiver-operating characteristic (ROC) curve. Subsequent multivariate analysis was done for all the factors with $P<0.1$. P value < 0.05 was considered statistically significant.

Results

Of 240 infants, 113 (47%) were males, and 127 (53%) were females. The mean birth weight of the total sample was 1218.5 gm. Retinopathy of prematurity was absent in 175 (73%) and was present in 65 (27%) of the screened infants. For these 65 infants mean GA was 28.6 wks, the mean BW was 841 gms, 14 (21.5%) pts had stage 1 ROP, 37 (56.9%) had stage 2 without

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plus disease, 3 (4.6%) had stage 2 with plus disease, 11 (17%) had stage 3 with plus disease, and none of the patients had stage 4 or stage 5 disease (Table I). Birth Weight wise distribution of ROP pts (n =65) was 17 (26.2 %) infants were Less than 1 kg, 42 (64.6 %) were between 1 to 1.5 kg, 6 (9.2%) were between 1.6 to 2 kg (Table II). Table III shows the gestational age-wise distribution of infants with prematurity retinopathy. Infants with ROP had lower Birthweight (BW) (P <0.001) and GA (P<0.001). More infants with ROP had body weight <1000g and gestational age of fewer than 29 weeks compared to infants without ROP. Infants with ROP were noticed to have a significantly lower mean weight gain on postnatal day 28 (364.1 g; p < 0.001) compared to infants with no ROP (512.8 g). Moreover, RWG at the 2nd and 4th weeks was also lower (p <0.001 and p <0.05, respectively) in infants with ROP than with no ROP. (Table IV).

Cut-off values for RWG at the second week and GA for prediction ROP requiring treatment were 2.96 g/kg/d (95% CI 0.59–0.82, P < 0.05) and 29.6 w (95% CI 0.77-.95, P< .001) respectively.

According to multivariate analysis, independent risk factors of severe ROP that required laser treatment were GA < 29.6 w (P<.01) and RWG less than 2.96 g/kg/d after the second week of life. The adjusted odd ratio for RWG and low birth weight (LBW) infants are summarized in Table V.

Table I: Stage-wise distribution of ROP patients (n=65)

Stage	No. of patients	Percentage
Stage 1	14	21.5%
Stage 2 without plus	37	56.9%
Stage 2 with plus disease	3	4.6%
Stage 3 with plus disease	11	17%
Stages 4 and 5	None	None

Table II: Birth weight wise distribution of ROP patients (n=65)

Stage	No. of patients	Percentage
Less than 1 kg	17	26.2%
1 kg to 1.5 kg	42	64.6%
Greater than 1.5 kg	6	9.2%

Table III: Gestational age wise distribution of ROP patients (n=65)

Gestational age(weeks)	No. of patients	Percentage (%)
<28	9	13.8%
28-30	35	53.8%
31-32	9	13.8%
33-34	6	9.3%
>34	6	9.3%

Table IV Clinical and demographic characteristics of infants

	No retinopathy of prematurity n=175	Presence of retinopathy of prematurity n=65	P-value
GA (w) (min-max)	31.4 (26-35)	28.6 (25-32)	<.001
BW (g) (min-max)	1196 (581-1895)	841 (521-1341)	<.001
Mean Postnatal WG (g) at 28 days (min-max)	512.8 (80.0-1096.2)	364.1 (8.0-932.0)	<.001
RWG for 2 weeks (g/kg/d)	4.3	1.2	<.001
RWG at 4 weeks (g/kg/d)	11.7	8.3	<.05
relative weight gain (RWG), weight gain (WG), Gestational age (GA)			

Table V Multivariate analysis of the risk factors for severe ROP

	OR	95% CI	P-value
ELBW (< 1000g)	4.7	1.43-15.55	<.05
RWG (< 2.96 /kg/d)	3.95	1.31-12.21	<.05

Discussion

In most cases, ROP is mild, does not require any intervention, and regresses independently, but the severe form may lead to visual impairment. Low birth weight infants are primarily affected by this disease (Zhang et al., 2021). In a study done in Canada, it was predicted that lesser gain in weight in the postnatal period might be a predictor of ROP (Li et al., 2019). In our study, 27% of infants had ROP, similar to our study findings in one study in Singapore, which showed the incidence of ROP in deficient birth weight babies as 29.2% had a median gestational age of onset as 35 weeks (31-40 weeks) (Shah et al., 2005). Whereas a study done by Taqui AM in Pakistan reported a higher prevalence of ROP. In this Pakistani study, the ROP prevalence was 32.4% (Taqui et al., 2008). Another observational study conducted in Tehran showed that the incidence of ROP was 33.3% (Modrzejewska et al., 2022). Facts can be explained as these studies involved only deficient newborns of less than 32 weeks of birth weight. The majority of preterm infants have many comorbidities. Moreover, ethnicity also impacts the severity of the disease;

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Asian newborns are at an increased risk of severe ROP than others (Modrzejewska et al., 2022).

In the current study, poor weight gain at 28 days was highly associated with the occurrence of ROP; it was in line with the findings of a previous study conducted in Croatia (Šarić et al., 2020). Our study identified lower relative weight gains in the 2nd and 4th weeks as a noticeable risk factor for ROP, as in a Korean study by Wongnophirun et al., 2020). At the 2nd week of age, poor relative weight gain was considered an independent risk factor for severe ROP requiring laser treatment. The cut-off value of RWG (Wongnophirun et al., 2020) predicted severe ROP in our study was less than 2.96 g/kg/d after the second week of life in contrast to the reported by the previous studies (Cagliari et al., 2019; Hellström and Hård, 2019); it implies that local statistical data should be used for predicting cut off values. It was also observed for the WINROP model that used post-natal weight gain, weekly IGF-1, gestational age, and birth weight to predict proliferative ROP (Sjöbom et al., 2021). The sensitivity of this model was reduced from 100% to less than 90% when applied in other regions. In addition to RWG at 2nd week of life, low birth weight and low gestational age were independent risk factors. The presence of these risk factors is considered an indicator for screening. Poor postnatal weight gain is related to severe ROP and can be used as a predictive tool clinically as the body weight of the newborn is routinely measured and RWG is easily calculable. Our study had some limitations. First, being an observational study data of some patients was missing due to referral out or death. Second, it was a single center study with small sample size.

Conclusion

The presence of retinopathy of prematurity was associated with low postnatal weight gain in addition to low birth weight and gestational age.

Conflict of interest/disclosure

Authors have no conflict of interest.

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