ORIGINAL RESEARCH

Poor post-natal weekly weight gain as predictor of development of "Retinopathy of Prematurity" in preterm neonates

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is disorder of developing retinal blood vessels in premature infant retina. Several risk factors are associated with development of ROP.We aimed to assess whether poor postnatal weight gain is significant predictor for development of ROP. **Objectives:** To assess postnatal weight gain alone as predictor of ROP and to co relate other risk factors and poor postnatal weight gain as a predictor of ROP. **Methodology:** Prospective observational study was conducted on 101 preterm neonates ≤34 weeks and ≤ 2000g admitted to Level III Neonatal intensive care unit (NICU) of tertiary referral Medical College Hospital in Central Karnataka ,South India and fitting into inclusion criteria from 1st February 2021 to 31st November 2022.All neonates were screened for ROP at eligible postmenstrual age as per national guidelines and early morning, prefeed, nude weight of the baby and weekly postnatal weight gain were recorded.ROP was done using RetCam by ophthalmic technician and reported by ophthalmologist remotely.Data was collected and co related with ROP diagnosis using logistic regression.**Results:** Of 101 neonates, 18 of them developed ROP. Preterm neonates with ROP had significantly lower mean relative weight gain (41.5± 3.5g) than neonates without ROP(87± 2.8 g) ,p<0.001.In our study 17 out of 18 neonates who developed ROP had mean weekly weight gain of <100 g (p=0.02).Relative weekly weight gain < 100 g was associated with higher risk of developing ROP with odds ratio of 0.94.Logistic regression model with risk factors, non-administration of antenatal corticosteroids to mother ,gestational age, birth weight, prolonged oxygen therapy and low weekly weight gain < 100 g was statistically significant and explained 43 % variance in ROP development, correctly classifying 88.1 % cases.**Conclusion:** We can conclude that poor postnatal weekly weight gain < 100g is significant risk factor and useful predictor for development of ROP.

Keywords: Retinopathy of prematurity (ROP); RetCam; Postnatal weight gain.

INTRODUCTION

Retinopathy of prematurity (ROP) is disorder of developing retinal blood vessels in premature infant retina. Peripheral retinal neovascularization is the primary pathology in ROP. Outcome of this is complete regression or sequelae ranging from mild myopia to bilateral total blindness.

Terry[1,2] in 1942 first described it as retrolentalfibroplasia[1] – "fibroblastic overgrowth of the persistent tunica vasculosalentis". [3]Over 22% of childhood blindness in India is attributable to Retinal etiologies of which ROP is commonest. It is preventable cause of blindness. [4]

ROP incidence in India is around 38-51.9% in low birthweight infants. [4] Out of 27 million newborns born every year, 8.7% (2 million) weigh <2000g and are at risk of developing ROP .[5]

WHO suggests that developing countries including India are suffering from an epidemic of ROP. Owing to improving neonatal care in our country more premature newborns are surviving now than they did before and hence are prone to this "new epidemic".[6]

This is result of, firstly, improved newborn care and survival. Secondly, supplemental oxygen is not used judiciously. Thirdly, all neonates receiving supplemental oxygen are not adequately monitored as per gestational age based set target saturations. Lastly, screening and treatment guidelines are not available in many cities.[7]

ROP has multifactorial etiology. Post-natal risk factors are prematurity, use of surfactant, low birth weight, oxygen-therapy,sepsis,blood transfusion, and intraventricular hemorrhage . [5,6]

Depleted plasma concentrations of IGF-I lead to poor weight gain in the post-natal period. Hence post-natal weight gain is a marker of serum IGF-1 levels. These are being recognized as significant risk factors from the newer studies.[8]

Larger neonates with higher gestational age and birth weight with other risk factors like oxygen supplementation and sepsis have been found to develop ROP but due to screening criteria there is a paucity in screening these neonates and fall prey to ROP. Due to resource limitation and lack of awareness in developing countries, neonates might not undergo screening for ROP hence the need for development for easier screening tools like poor postnatal weekly weight gain especially for resource limited centers which will enable early referral for ROP screening.

MATERIALS AND METHODS

This was explorative observational study done prospectively on 101 inborn preterm neonates admitted to our Level III NICU of Medical College Hospital in Central Karnataka, South India and meeting inclusion criteria for ROP based on Rashtriya Bal SwasthyaKaryakram(RBSK) guidelines[9] between 1st February 2021 to 31st November 2022. The inclusion criteria were neonates born at ≤ 34 weeks of gestational age ,birth weight ≤ 2000 gramsor neonates born with birth weight > 2000 grams and > 34 weeks and presence of other risk factors like oxygen therapy**,** ventilation**,** exchange transfusion**,** blood products use**,** hyperbilirubinemia**,** apnea**,** **s**epticemiaand CPAP. Those neonates of gestational age ≤ 34 weeks and birth weight ≤ 2000 grams with life threatening congenital anomalies were excluded. As it is an exploratory study, sample size of convenience was considered.

A detailed history including birth weight, gestational age at birth, weight for gestation, weekly weight gain and problems during NICU stay were recorded in pre structured proforma.

ROP screening was done after dilating the pupils using 0.4% Tropicamide + 1.25% Phenylephrine eye drops, under the guidance of neonatologist, by expert ophthalmic technician using RetCam (3nethra Neo, Forus Health Ltd., India, 2018) which was reviewed and reported by an ophthalmologist in a remote location. The initial examination was done at 4 weeks after birth or 31 to 33 weeks post conceptional age , whichever was later. The follow up was carried on until completion of ROP screening or 40 weeks of corrected gestational age. Early morning, pre-feed, nude weight of the baby was measured using weighing scale (Essae – DS - 252, India) with an accuracy of ± 20 grams and recorded in the case proforma. Weekly weight gain was recorded. Weekly weight gain <100g was considered as poor weight gain. The need for further follow up until postconceptional age of 40 weeks was advised. Serial monitoring of the post-natal weight was done during the follow up for 7 weeks. Study was conducted after obtaining the Institute Research Ethics Committee approval (Protocol No. Sy-42-2021) as per principles of Declaration of Helsinki . Written informed consent was obtained from neonates' parents who were eligible for enrolment into study.

Statistical Analysis

As it was an exploratory observational study, a sample size of convenience was considered. Data was analyzed using SPSS version 23.0(SPSS Inc., Chicago, USA). Categorical variables were expressed as frequencies (percentages) and continuous variables as mean ± SD and Median (IQR). Chi square test was applied for comparison of various risk factors for the development of ROP between independent groups. p value <0.05 was considered statistically significant. Logistic regression was done to assess whether weekly weight gain < 100 g was a significant predictor for the development of ROP along with other risk factors such as non-administration of antenatal corticosteroids to mother, gestational age, birth weight and prolonged oxygen therapy .

RESULTS

Maternal demographic variables

55 (54.5%) neonates were born to a primigravida mother.45.5 % of mothers of recruited preterm neonates(n=101) did not receive antenatal steroids. Amongst neonates who developed ROP(n=18) ,16% of mothers had not received antenatal corticosteroids.

Neonatal demographic variables are depicted in ***Table. 1***.Mean GA was 34.5 ±2.8 weeks and mean Birth weight was 1557.1±32.7 g in our study population**.**

Table 1: Neonatal demographic variables

Neonatal Parameters	Values
Type of pregnancy - Singleton	77 (76.24) #
Gender - Male	64 (63.37) #
IUGR	7 (6.93) #

APGAR at 1’	5.76 ± 0.95 *
APGAR at 5’	7.55 ± 0.66 *
Gestational age (in weeks ± days)	34.5 ± 2.8*
Birth weight (in gram)	1557.1 ± 32.7*
Duration of oxygen administration (in hours)	48 (12, 96) **
Duration of respiratory support (in hours)	24 (0, 60) **
Sepsis	72 (71.2) #
Anemia	28 (27.73) #
Hemoglobin (in g/dL)	14.15 ± 4.03*
Platelet count (in cells / cu mm)	90000 (35000, 213000) **
NNHB	81 (80.2) #
Maximum TSB	10.86 ± 3.05*
Duration of phototherapy	48 (48, 72) **
Age of initiation of feeds	4.59 ± 2.41 *
Age at reaching full feeds	15.8 ± 6.55 *
Apnea	38 (37.62) #
Administration of caffeine	31 (30.7) #
DVET	2 (1.98) #

Values in #n(%), *mean ± SD, ** median (IQR)

Neonatal risk factors

The most common risk factor was neonatal hyperbilirubinemia (NNHB) (n=81) of which 18(22%) developed ROP as shown in ***Fig.1.*** Two neonates that underwent Double Volume Exchange Transfusion for severe hyperbilirubinemia developed ROP.

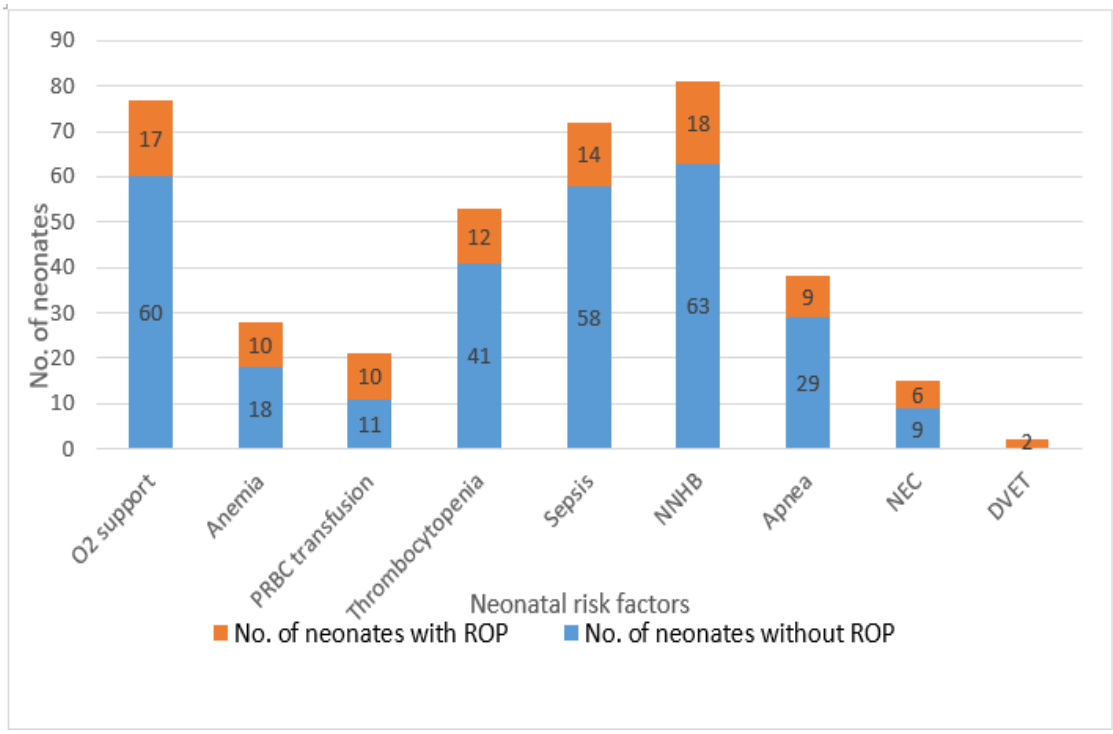

Figure I: Distribution of neonates based on risk factors and development of ROP

Of the risk factors studied, six were found to be statistically significant for development of ROP. They were non -administration of antenatal steroids ($p<0.01$), birth weight ($p=0.03$), prolonged respiratory support ($p=0.02$) provided during the NICU stay, PRBC transfusion ($p<0.01$), NEC ($p=0.01$) and post-natal weekly weight gain < 100g ($p=0.02$). GA with $p= 0.057$ had a trend towards significance for development of ROP.

The other risk factors studied were sepsis, NNHB requiring phototherapy and apnea, all of whose p-value was found to be > 0.05.

Comparison of the gestational age, birth weight, weekly weight gain trends and average of the relative weight gain is depicted in ***Table II***. It can be understood that the mean gestational age, mean birth weight was lesser for ROP group (29.6±1.7 weeks,1310±28 g) than that of the no ROP group

(33.3 ±1.33 weeks,1609±31g). The mean relative weight gain was much lesser among the ROP group than the no ROP group.

Table II: Comparison of risk factors between neonates who developed ROP and those without ROP

Risk Factors	ROP (n=18)	NO ROP (n=83)	p-value
Mean gestational age *(weeks)	29.61 ± 1.72	33.39 ± 1.33	0.05*
Gestational age			
• < 28 weeks	0	0	
• 28 + 1 to 30 weeks	4	5	
• 30+1 to 32 weeks	7	14	
• 32 + 1 to 34 weeks	3	31	
• 34 + 1 to 36 weeks	4	24	
• >36 weeks	0	6	
Mean birth weight *(g)	1310 ±28	1609 ± 32	**0.03***
Birth weight (in g)			
• < 1000	2	1	
• 1001 – 1500	12	31	
• 1501 – 2000	4	43	
• 2001 – 2500	0	7	
• > 2500	0	1	
Average relative weight gain			
• < 100g	17	1	**0.02***
• > 100g	30	53	
Sepsis			
• Present	14 (77.78)	58 (69.88)	0.50
• Absent	4 (22.22)	25 (30.12)	
Respiratory support			**0.02***
• No support	1 (5.56)	23 (27.71)	
• Head box	4 (22.22)	21 (25.3)	
• CPAP	5 (27.78)	28 (33.73)	
• Mechanical ventilation	6 (33.33)	11 (13.25)	
• NIPPV + MV	2 (11.11)	0 (0)	
PRBC transfusion			
• Given	10 (55.56)	11 (13.25)	**< 0.01***
• Not given	8 (44.44)	72 (86.75)	
Phototherapy			
• Given	16 (88.89)	64 (77.11)	0.26
• Not given	2 (11.11)	19 (22.89)	
Apnea			
• Present	9 (50)	29 (34.94)	0.23
• Absent	9 (50)	54 (65.06)	
NEC			
• Present	6 (33.33)	9 (10.84)	**0.015***
• Absent	12 (66.67)	74 (89.17)	
Antenatal steroids			
• Given	15 (83.33)	40 (48.19)	**< 0.01***
• Not given	3 (16.67)	43(51.81)	

*****p-value statistically significant

Table III: Comparison of risk factors among ROP and No ROP group

ROP status	Mean Gestational age (In weeks ± days)	Mean Birth weight (In g)	Mean relative weight gain (in grams)				Mean of relative weight gain (in grams)	Duration of oxygen administration (In hr) (Median, IQR)	Duration of respiratory support (In hr) (Median, IQR)	Mean hemoglobin (In g/dL)	Mean maximum TSB (mg/dl)	Duration of phototherapy (In hr) (Median, IQR)	Mean time of initiation of feeds (in days)	Mean time of reaching full feeds (in days)
			Week 1	Week 2	Week 3	Week 4								
ROP	29.61 ± 1.72	1310 ± 282.35	-86.11	18.33	41.11	67.78	41.58	96 (53.5, 153)	58 (29.5, 78)	11 ± 4.4	12.0 ± 4.61	84 (48, 96)	5.5 (4, 7.75)	17.5 (12, 23.5)
No ROP	33.39 ± 1.33	1609± 313.38	-67.56	59.6	82.28	105.8	87.13	48 (0, 78)	36 (0, 49)	14.8 ± 3.5	10.6 ± 2.56	48 (30, 72)	3 (2, 4)	12 (9, 15)

The mean relative weekly weight gain and the mean of the relative weight gain were found to be lesser in the ROP group when compared to the no ROP groupas shown in***Table. III.***ROP group had later inititian of feeds and reached full feeds 5 days later as compared to No ROP group.

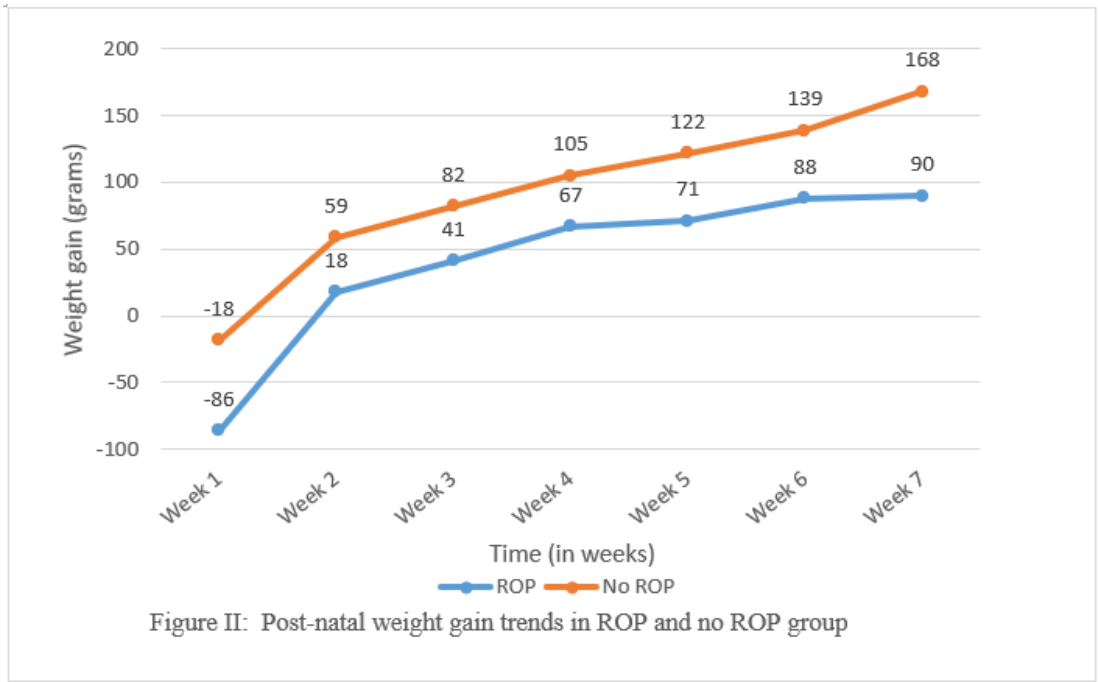

Figure II: Post-natal weight gain trends in ROP and no ROP group

Figure II: Weekly post-natal weight gain trends of neonates with ROP and neonates without ROP.

Figure. II represents the post-natal weight gain trends of neonates with ROP and neonates without ROP. Initial weight loss is attributed to the physiological process. In this graph we can notice that the mean weight gain in the subsequent weeks was lesser in the ROP group when compared to the neonates without ROP (p-value < 0.001). Preterm neonates with ROP had significantly lower mean relative weight gain (41.5± 3.5g) than neonates without ROP (87± 2.8 g), p<0.001. In our study 17 out of 18 neonates who developed ROP had mean weekly weight gain of <100 g (p=0.02).

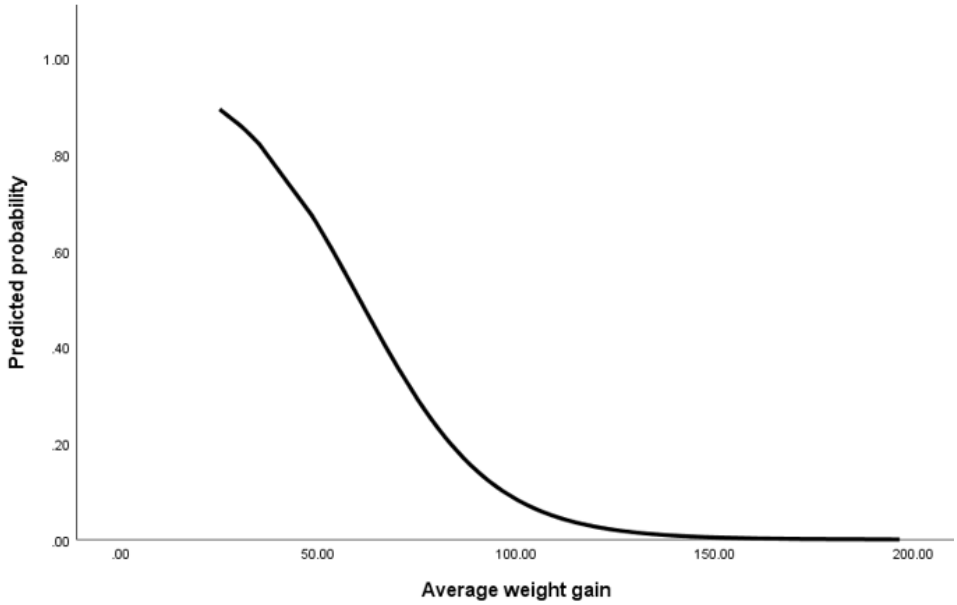

Figure III: Binomial logistic regression to ascertain effect of weight gain on the development of ROP

Figure. III depicts the binomial logistic regression done to ascertain the effect of weight gain on the development of ROP. The logistic regression model was statistically significant with χ^2 (df1) = 34.311, p < 0.05. The model explained 47.3% (Nagelkerke R^2) of the variance in development of ROP and correctly classified 88.1% of cases.

Sensitivity of the model was 55.55%, specificity was 95.18%, positive predictive value was 71.43% and negative predictive value was 90.8%. The odds ratio is 0.941 which means that inadequate weight gain is associated with higher risk of development of ROP.

A multivariate analysis was performed and it was inferred that non administration of antenatal steroids to mother and poor post-natal weekly weight gain <100g were the two variables which were found to be significant risk factors for development of ROP.

DISCUSSION

In our study on 101 eligible preterm neonates, conducted in Level III NICU of a tertiary referral medical college hospital in South India between February 2021 to November 2022, we have studied the poor post-natal weekly weight gain and the other neonatal risk factors as a predictor of ROP. Preterm neonates with ROP had significantly lower mean relative weight gain (41.5± 3.5g) than neonates without ROP (87± 2.8 g), p<0.001. In our study 17 out of 18 neonates who developed ROP had mean weekly weight gain of <100 g (p=0.02). Relative weekly weight gain < 100 g was associated with higher risk of developing ROP with odds ratio of 0.94. Significant risk factors for ROP development were found to be birth weight, need for oxygen and respiratory support, administration of PRBC transfusion, relative poor weekly weight gain in the post-natal period, non-administration of antenatal steroids to the mother and NEC. Amongst neonates who developed ROP(n=18), 16% of mothers had not received antenatal corticosteroids.

In our study, gestational age was not significant risk factor however had trend towards significance. This is attributed to the small sample size. A study by Subramanya P. *et al.*[10], reported mean gestational age and birth weight lesser when compared to the mean gestational age and birth weight of our study. However relative post-natal weight gain was found to be similar. The other variables which were found to be significant in this study and similar to our study were the need oxygen during NICU stay and the requirement for PRBC transfusion.

Study by Filho *et al*., reported a mean gestational age (29.6 ± 1.9 weeks) and mean birth weight (1124 ± 239.5g) which were similar when compared to our study while the weight gain was taken between week 1 and week 6 so the average weight gain for six weeks was noticed to be 597 ± 218.1g (~99.5g/week) [11]which is <100g per week and is similar to our study. In this study there were no other risk factors that were found to be significant in comparison to our study. A study in Spain by Canabas Poy *et al.*[12], had a mean gestational age and mean birth weight similar to our study with an average weight gain of 776 ± 298 g (~ 129.34 g/week).

Wallace *et al.*[13] reported a mean gestational age of 27.2 ± 1.9 weeks and a mean birth weight of 948 ± 267g which are much lesser when compared to those in our study. This could be attributed to the fact that due to better health care facilities and lesser cut off for viable pregnancies in the US. The average weekly weight gain in the ROP group was found to be 78.7 ± 37.4g which is < 100g and is similar to our study. The other risk factors that were studied were oxygen requirement, blood transfusion and sepsis of which the latter two were significant risk factors.

A study by Aydemir O. *et al.*[14], had mean GA (29.3 ± 2.3 weeks) and mean BW (1165 ± 223g) lesser when compared to our study. The other risk factors were oxygen requirement, PRBC transfusion, sepsis and NEC, all of which were found to be significant risk factors similar to our study.

Study by Chaudhari *et al.* showed baseline characteristics similar to our study with comparable mean GA (31.4 ± 2.2 weeks) and mean BW (1306 ± 267g). The other risk factors which were significant in the development of ROP were oxygen requirement and sepsis.[15]

Kumar *et al.* and Patel *et al.*, had comparable mean GA (30.62weeks) and mean BW (1043g). The other significant risk factors in these studies were oxygen requirement, sepsis and oxygen requirement, sepsis, PRBC transfusion, administration of antenatal steroids respectively.[16,17]

The strengths of our study were that along with poor weekly weight gain other risk factors were studied simultaneously as a predictor of development of ROP. As this is an Indian study, it can be comparable to neonates of the developing countries due to similar baseline characteristics and such studies are important in remote, resource limited setup. This study also insists on the meticulous screening of neonates for ROP not only based on gestational age and birth weight (which were the older parameters used) but also based on other risk factors like oxygen administration, poor weekly weight gain, NEC and administration of PRBC transfusion.

The limitations of our study was small sample size. Larger sample size could help better in validating the objectives of this study.

CONCLUSION

We can conclude that poor post-natal weekly weight gain is significant risk factor and can be used as predictor of development of ROP. In resource poor settings where ROP screening service is not readily available, poor post-natal weight gain can be considered as a red flag sign for early referral to an ophthalmologist for ROP screening. As a future direction, development of an Indian ROP Predictor Algorithm using weekly weight gain and other significant factors for ROP such need for oxygen and respiratory support, non-administration of antenatal steroids in the mother, PRBC transfusion and NEC can be developed to enable early referral for ROP screening.

Hence this study recommends that neonatologists and ophthalmologists should pay attention to those neonates with poor post-natal weight gain and subject them to early screening of ROP and management with appropriate follow-up.

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