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A LONGITUDINAL STUDY ON SERUM INSULIN-LIKE GROWTH FACTOR-I (IGF-I) LEVELS IN INFANTS AND ITS CORRELATION WITH INCIDENCE OF RETINOPATHY OF PREMATURITY.

Dr. Raghu T Gokhale[1], Dr. Pradeep GCM[2], Dr. Krithika MV[3*], Dr. Sharanabasavesh M[4], Dr. Mallikarjuna B[5]

[1]Junior Resident, Department of Pediatrics, Ramaiah Medical College
[2] Professor of Pediatrics, Ramaiah Medical College
[3]Assistant Professor, Ramaiah Medical College
[4]Associate Professor, Ramaiah Medical College,
[5]Professor of Pediatrics, Ramaiah Medical College, Bangalore.

***Corresponding author:** Dr. Krithika MV
*MD, DM (Neonatology), Assistant Professor (Neonatology), Ramaiah Medical College, Bangalore.

Abstract:
Retinopathy in premature infants is still a cause of concern in lower- and middle-income countries. Preterm infants with lesser post-natal weight gain during first 4weeks and lower serum IGF-1 level have higher incidence of ROP. This study focusses on correlation of post-natal weight gain pattern and serum IGF-1 level with incidence of ROP among South Indian population. It included two cohorts of preterm infants with and without ROP ≤32 weeks gestational age / ≤1500gm birth weight. Serum IGF-I levels were measured at the end of 28days. Data was analysed to observe significant difference in mean weight gain pattern of with and without ROP group. The cohort without ROP had a better weight gain pattern and better IGF-1 levels as compared to the cohort with ROP. Weight gain was shown to be an independent predictor (p value: 0.012) after comparing the various other risk factors by logistic regression. The mean duration of age of reaching full feeds in the two groups shows a significant difference {15.57(6.204) in the group without ROP as compared to 19.62(6.775) in the group with ROP} p= 0.008. Mean serum IGF-1 levels of the two cohorts signified that the cohort without ROP had better serum IGF-1 levels as compared to the cohort with ROP. Cumulative weight gain was the only independent risk factors for severe ROP. Thereby, promotion of postnatal growth and weight gain along with optimal nutrition might prevent proliferative ROP in infants.

Keywords: Retinopathy of prematurity; preterm infant weight gain; IGF-1; postnatal growth; nutrition.

1. Introduction

Retinopathy of prematurity (ROP) is the second leading cause of preventable childhood blindness globally. However, severe ROP leads to permanent vision loss and retinal detachment. ROP incidence in India is around 38-51.9% among the low-birth-weight infants. Of the 26 million live births

annually, 8.7% of newborns weight <2000gms implying an estimated risk of developing ROP for around 2 million newborns[1].

ROP is associated with multiple systemic risk factors with poorly understood etiology and pathogenesis. Major risk factors for ROP includes immaturity of newborn infants with low birth weight and low gestational age, and prolonged mechanical ventilation[2]. Detachment of retina and scarring due to disorganized growth of retinal blood vessels were reported to be the causative factors for ROP. It occurs when vascularisation halts and proceeds abnormally with fibrovascularisation. Subsequently, the lack of insulin-like growth factor 1 (IGF-1) is reported for its pivotal role in normal growth and development of many tissues, such as brain and blood vessels.

Standard guidelines employ gestational age and birth weight as markers for ROP to examine treatable disease in infants [3]. Weight gain patterns after birth have been noted to be key predictor of ROP at less than 28 days of age. This study focusses on investigating the correlation of postnatal weight gain and serum IGF-I level with ROP.

2. Methods

2.1. Subjects' inclusion and exclusion

Subjects were prospectively recruited between January 2019 and December 2019 at the Neonatal Intensive Care, Ramaiah Medical College, Bangalore. The subjects included were preterm infants with a gestational age ≤ 32 weeks or a birth weight ≤ 1500 g who stayed in NICU for minimum period of 4 weeks and had been screened for ROP [4]. Preterm infants who got discharged or died before 4 weeks of life were excluded from the study. Those neonates who were lost for follow up for ROP screening, and outborn neonates admitted after 48hrs of life were also excluded. The Study protocol was approved by the institutional ethics committee.

2.2. Assessment of risk factors

All neonates admitted in NICU received standard care as per the unit protocol. Assessment of gestational age was performed as per LMP or first trimester USG scan (if disparity found) supported by gestational assessment done by two trained residents and a consultant in the NICU within first 24 hours of birth using Modified Ballard's Score. While administering supplemental oxygen, SpO_2 was maintained between 91-95%. On signs and symptoms of radiological features of RDS, surfactant (100 mg/kg) replacement therapy was given. Continuous positive airway pressure (CPAP) was given in case of mild to moderate respiratory distress.

2.3. Feeds, blood culture and transfusion requirements

Neonates with no risk factors & haemodynamically stable were started on trophic feeds on day 1 of life and gradually increased. Blood culture was taken at admission if there were clinical features or laboratory parameters suggestive of sepsis or if neonate is at high risk of sepsis. Antibiotics were continued till culture was sterile at 72hrs post inoculation. In case of culture positivity antibiotics were changed according to culture sensitivity pattern. Transfusion of packed red blood cells was suggested in case of <21% Hct in asymptomatic infants, <31% Hct in infants requiring prolonged Fio2, and frequent apnoeic episodes. Platelets were transfused in case of asymptomatic infants with platelet count <20,000 cells/cu.mm, and in infants with signs and symptoms of bleeding.

2.4. Ophthalmic examination

Ophthalmic examination was done by single examiner with all aseptic precautions with indirect binocular ophthalmoscope in a 20 diopters lens. 0.5% tropicamide and 2.5% phenylephrine were used to dilate pupils. For infants born ≥ 28 weeks of gestational age, first retinal examination was performed at 4 weeks. While for Infants born <28 weeks or <1200 grams birth screening was performed early, by 3 weeks of age as per NNF clinical practice Guidelines 2010 [5]. A major outcome was ROP incidence in either eye, recorded as per international classification of ROP. Accordingly, severe ROP was defined as Type 1 ROP as recorded in ETROP study or threshold disease [6].

2.5. Weight gain assessment

Neonates were daily weighed unclothed using the same weighing scale once a day before feed. Head circumference and length were recorded weekly. Weight of the newborn on each day from birth till 4 weeks was noted as in the records. Weight gained (cumulative) over the 4 weeks was measured as the difference between the weight of the infant at birth and at the end of 4 weeks. Weight gained at the end of each week was also recorded. Time taken to regain the birth weight was calculated. Growth curves were used to assess the longitudinal growth of the infants up to 4 weeks which included the birth weight, daily weight, weekly weight gain and the total(cumulative) weight gain.

2.6. Cumulative assessment of weight gain, ROP and serum IGF-I

The duration of TPN, days taken to achieve full feeds and Serum IGF-1 levels (ng/ml) at the end of 28 days, post-natal daily weight, post-natal 1st, 2nd, 3rd, and 4th weekly weight gain pattern, cumulative weight gain at the end of 28 days/4th week, age at which birth weight was regained were also recorded.

Based on a study conducted by Hellstrom et al. (2009) it was found that 36% of infants were at no risk of ROP and 24% had a risk of developing severe ROP out of 353 infants screened. So, with the desired confidence of 95% and a risk difference of 0.12, sample size was 35 in both the groups [7].

Totally, a cohort of 35 preterm infants who had no or stage 1 ROP were compared with a cohort of 42 preterm infants who had developed stage 2 and above ROP. Mean weight gain of the infants in the two cohorts over 4 weeks from birth were calculated as a measure of post-natal weight gain pattern and the measurement of serum IGF-I levels at the end of 28 days stay in the hospital. The serum IGF-I level were measured by collecting 0.5 ml of venous blood samples taken at the end of 4th week/28days. All the samples were analysed using ELISA DRG® IGF-1 600 ELISA (EIA-4140) kit.

2.6. Statistical analysis

Continuous variables with normal distribution were subjected to Student ‘t’ test while for variables with skewed distribution Mann-Whitney U-test was performed. Categorical variables were subjected to Chi square test. For variables significant on univariate analysis logistic regression analysis was performed.

3. Results

Overall, 1599 neonatal admissions were recorded in the study period. Of these, 246 were preterm infants with ≤32 weeks gestational age and/or ≤1500 g birth weight. Out of 246, 132 were discharged before 28 days, 33 were expired and 4 were lost to follow up. Totally, 77 infants were available for analysis who were categorised into two groups; Group 1 ROP n = 42 (54.5%) and Group 2 without ROP n = 35 (45.5%).

3.1. Demographics of birth weight in infants

Baseline clinical characteristics including weight at birth, gestational age and gender distribution were mentioned in table 1. Mean birth weight was 1.16 ± 0.22 kg and mean gestational age was 30.51 ± 1.9 weeks. There were 17 extremely low birth weight infants. 15 neonates were < 28 weeks at birth. Among all the infants with ROP only two were subjected to laser photocoagulation without any sequel. Regression of ROP was observed in all the infants following treatment.

Table 1: Baseline clinical characteristic of the study population.

S. no.	Parameters	Number of subjects (%)
1	Inborn	66(85.7%)
	Out born	11(14.3%)

3	Weight at birth in grams.	
	< 1 kg	17 (22.07)
	1-1.5 kg	60 (77.92)
5	Gestation age at birth in weeks	
	<28	15(19.5%)
	28 $^{+1}$ - 30	22(28.57%)
	30 $^{+1}$ -32	22(28.57)
	>32	18(23.4%)
6	Males	41 (73.2%)
	Females	36 (46.8%)

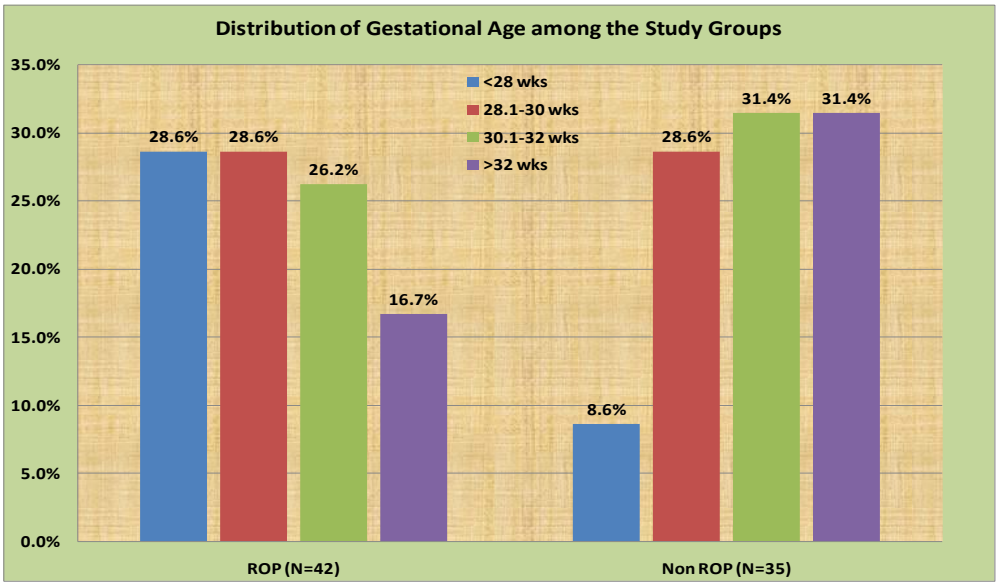

Figure 1: Distribution of gestational age among ROP and Non-ROP study groups.

3.2. Gestation age and ROP

ROP incidence in the study group was higher with a decrease in gestational age at birth. Incidence of ROP in ≤ 28weeks was 80% (12/15), at 28.1-30 weeks 54.54% (12/22), at 30.1-32 weeks 50% (11/22) and at >32 weeks 38.88.% (7/18). Nearly 10% of infants > 32 weeks of gestation had ROP.

The demographics of various studied parameters were mentioned in table 2. Among these, association of Apnoea incidence, PDA incidence, thrombocytopenia, platelet transfusion, packed red cells transfusion, mean period of gestation and mean period of CPAP with ROP were found to be statistically significant ($p<0.05$). Further, figure S1 indicate association of post-natal mean daily weight in the two study groups ($p<0.05$).

3.3. Weight gain and nutritional pattern between ROP and Non-ROP groups

Between the study groups, the longitudinal postnatal weight gain pattern was depicted in Figure 2, as recorded by a daily mean weight gain assessment (Figure S1). Results suggest a significant difference ($p<0.05$) between two groups in the weight gain pattern. Non-ROP group had a better weight gain pattern than ROP group. On analysing the feed pattern of infants, the cohort without ROP had younger age at reaching full feeds, and at regaining birth weight, and shorter duration of total parenteral nutrition (TPN) in comparison with the cohort with ROP (Table S1). The median age of reaching full feeds in the cohort without ROP was found to be 15.57(6.204) and 19.62(6.775) in the cohort with ROP ($p = 0.008$). Since the cohort without ROP reached full feeds earlier than the other group, probably it had a more aggressive nutritional supplementation. There is a significant difference ($p = 0.049$) in the mean duration of TPN received in the two groups (11(9.053) in the group without ROP as compared to 15.57(9.058) in the group with ROP) (Table S1).

Table 2: Showing the demographics of various parameters in the study groups.

S. no.	Risk factors	With ROP (No of infants) N=42	Without ROP (No of infants) N=35	P value
1	Surfactant requirement	22 (52.4%)	15 (42.9%)	0.405
2	Apnoea incidence	29 (69.0%)	14 (40.0%)	**0.011**
3	PDA incidence	13 (31.0%)	3 (8.6%)	**0.016**
4	Thrombocytopenia	20 (47.6%)	7 (20.0%)	**0.011**
5	Platelet transfusion	9 (21.4%)	2 (5.7%)	**0.050**
6	Packed red cell transfusion	19 (45.2%)	8 (22.9%)	**0.040**
7	Culture proven sepsis	6 (14.3%)	2 (5.7%)	0.220
8	Antibiotic ≥ 7 days	34 (81.0%)	27 (77.1%)	0.682
9	Mean Period of Gestation (weeks)	29.94 (2.470)	31.20 (2.602)	**0.033**
10	Mean Period of Supplemental O2 (hrs)	83.67 (102.217)	55.60 (64.095)	0.163
11	Mean Period of CPAP (hrs)	96.74 (125.138)	34.60 (51.494)	**0.008**
12	Mean Period of Invasive Ventilation (hrs)	33.00 (57.894)	11.71 (31.021)	0.055

3.4. Serum IGF-I levels between ROP and Non-ROP groups

Serum IGF-I levels were known to be a responsible measure to prevent ROP in preterm infants. In this study, serum IGF-I levels were studied longitudinally for a period of four-weeks among patients across one year. Accordingly, the mean serum IGF-1 levels of the two cohorts were depicted in Figure 3. Interestingly, the group with ROP had a mean serum IGF-I level of 9.03 ng/dl while the group without ROP had a significantly higher 44.94 ng/dl mean serum IGF-I levels.

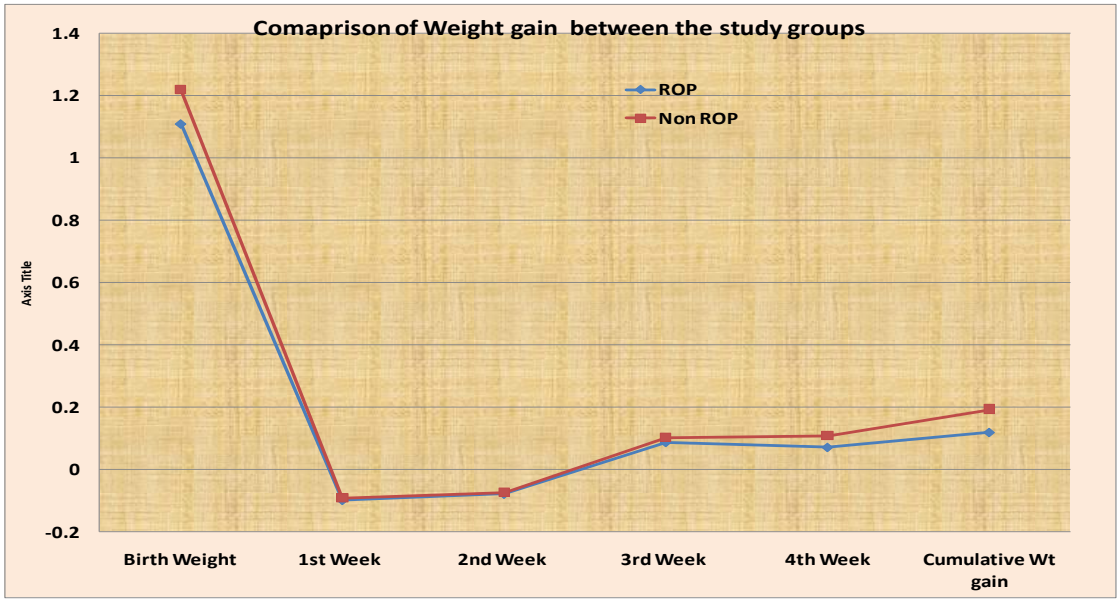

Figure 2: Post-natal weight gain pattern (mean weight gains each week and the mean total weight gain) in the two groups. Along x axis is the time in weeks from Birth weight, weight gain at 1, 2, 3, 4, weeks to total (cumulative) weight gain; along y axis is the mean weights in Kg.

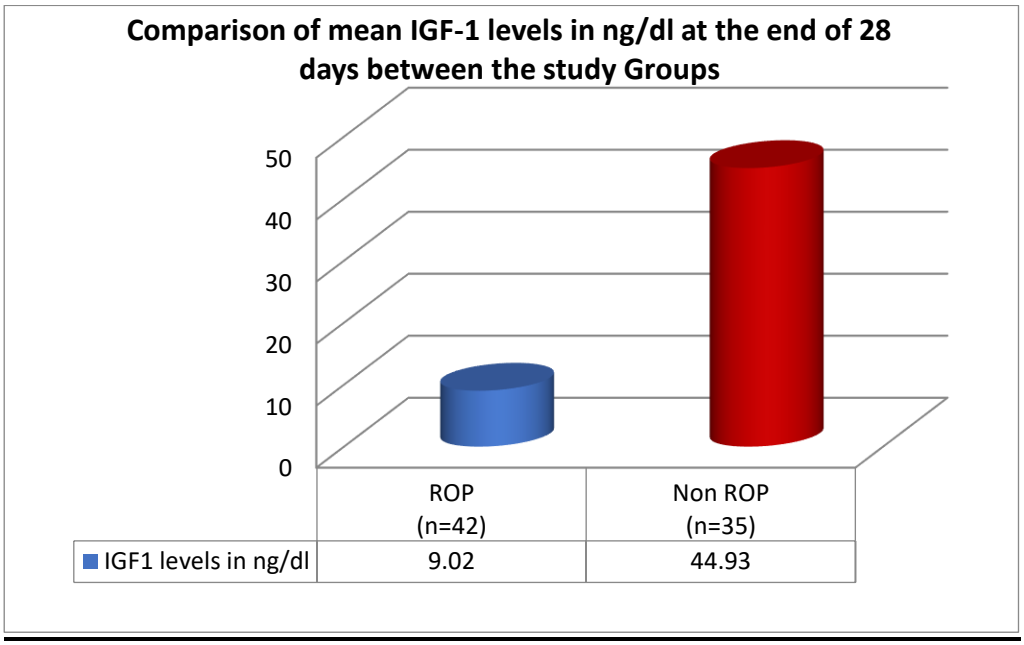

Figure 3: Comparison of mean IGF-1 levels (ng/ml) at the end of 28 days between the study groups.

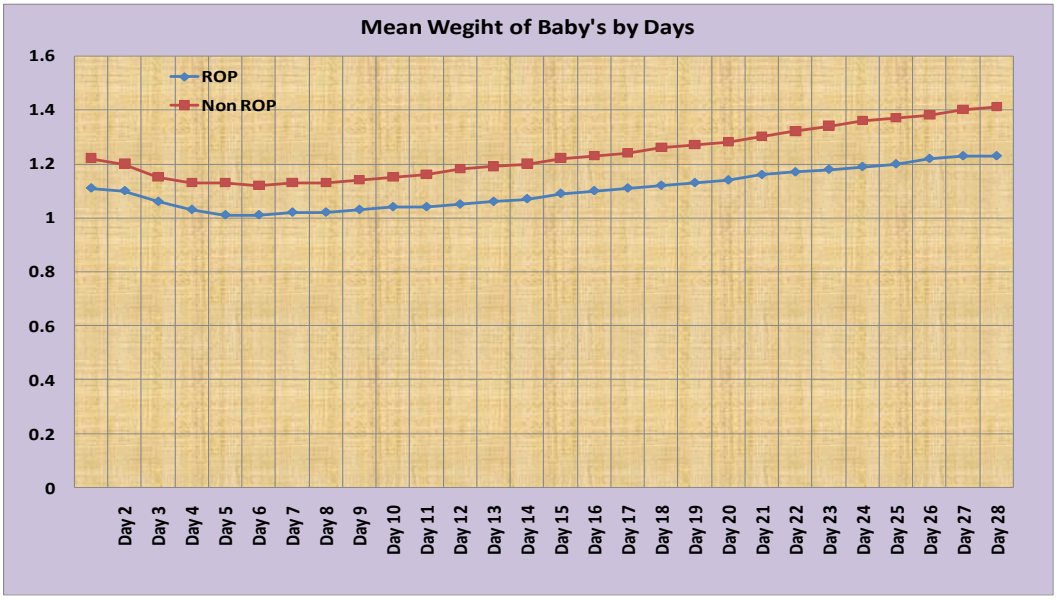

Figure S1: Post-natal mean daily weight in the two groups day by day.

Table S1: Showing the nutritional parameters in the study groups with and without ROP

S. no.	Risk factors	With ROP Mean (SD)	Without ROP Mean (SD)	P VALUE
1	Mean Age of Reaching Full Feeds (days)	19.62 (6.775)	15.57 (6.204)	0.008
2	Mean Days Taken to Achieve Full Feeds (days)	17.29 (6.649)	13.57 (6.279)	0.014
3	Age of regaining Birth weight (days)	18.19(6.448)	14.97(6.350)	0.031
4	Mean period of total Parenteral Nutrition (days)	15.57 (9.058)	11.43 (9.053)	0.049
5	Mean IGF-1 levels at the end OF 28 days (ng/ml)	9.02 (19.86)	44.93 (23.17)	0.001

3.5. Risk factors, Univariate analysis, Multivariate analysis and Logistic Regression

On univariate analysis apnoea incidence, PDA incidence, thrombocytopenia, platelet transfusion, packed red cell transfusion, culture proven sepsis, antibiotics ≥ 7 Days, mean period of gestation (weeks), mean period of supplemental O_2 (hours), mean period of CPAP (hours), mean period of invasive ventilation (hours), mean age of reaching full feeds (days), mean days taken to achieve full feeds (days), age of regaining birth weight (days), mean period of total parenteral nutrition (days) were found to be significant risk factors for ROP.

4. Discussion

Incidence of blindness after ROP in preterm infants is globally an increasing threat. Multiple weight-gain models including G-ROP, PINT ROP, CHOP ROP, CO_ROP, WINROP and ROPScore were reported in various studies to assess the severity of ROP. Nevertheless, according to 2018 policy statement from the American Academy of Paediatrics, standalone weight-gain algorithms are not justified based on current literature [8]. Hence, the present study analyses the weight gain pattern along with serum IGF-I levels and other clinical parameters such as apnoea incidence, PDA incidence, thrombocytopenia, platelet transfusion, packed red cells transfusion, mean period of gestation and mean period of CPAP in preterm infants between ROP and Non-ROP groups.

A study by Chaves-Samaniego et al. (2021) reported that the most significant risk factors for ROP based on previous studies includes gestational age, duration of mechanical ventilation, birth weight and neonatal comorbidities. The study also reported that the birth weight, PDA and cumulative weight gain were the independent risk factors to predict development of ROP [9]. A similar study reported gestation < 28 weeks, RDS and PDA as independent risk factors for ROP [10].

Incidence of ROP rises with decrease in birth weight. Poor weight gain pattern in infants during early postnatal period might pose high risk of developing ROP which needs treatment. In the present study incidence of ROP in low-birth-weight infants was 82.35% (14/17). In another study, incidence of any ROP in low-birth-weight infants was 32.8% [10]. Also, in the present study incidence of ROP in infants with birth weight > 1500 gm was 46.66% (28/60). In a study done by Chaudhari et al. the incidence of ROP in infants with birth weight between 1500-1999 g was 11.4%, which was lower than the present study [11]. Present study also observed that weight at birth was not an independent risk factor for ROP. A similar result was reported by Kumar P et al.in another study [10].

As observed, ROP incidence was high with reduction in gestational age. Nearly 10% of infants > 32 weeks of gestation have ROP. Similar result was reported in another study done by Chaudhari et al.[11]. In a study done by Kumar et al. the incidence of severe ROP in < 30weeks was 11.3% which was less than the present study (10). Similar study with the association of ROP with mean birth weight gain was published by Subramanya et al. [12].

IGF-1 is reported to be important for growth in infants for healthy tissues such as brain, normal retinal vascularisation and blood vessels [3]. The present study used the difference in postnatal weight gain pattern and serum IGF-I levels as a predictor of development of ROP. Including IGF-I levels makes the study cost effective however excluding the IGF- levels makes the study a simpler one with lesser stress on the infants. Thus, it can be concluded that weight gain and IGF-I levels could be utilised as an independent risk factor for predicting the development of ROP. Results from this study support that low weight gain is an indirect indicator of low IGF-1 levels and hence development of severe ROP.

A study by Biniwale M et al. suggested faster weight gain and higher IGF-I have positive correlation with development of ROP [13]. Also, post-natal weight gain and post-natal weight gain velocity were reported to be surrogate markers for IGF-I and development of ROP, respectively as analysed by G-ROP, WINROP and CHOP-ROP studies. Some of Asian studies such as by Vinekar et al. reported

that regaining birth weight faster reduces the risk of ROP development [14]. Similar studies suggest IGF-I levels as surrogate markers for severe ROP if levels are low.[15; 16]

The probable reason for the difference in weight gain between ROP and non-ROP was the difference in the nutrition received by the infants. It was found that infants without ROP had a younger age at reaching full feeds than in infants with ROP. Thus, it is possible that the cohort without ROP had accepted better nutritional supplementation early and hence better weight gain. It was also found that the cohort without ROP is healthier compared to the cohort with ROP with lesser need for surfactant requirement, antibiotics ≥7days and culture proven sepsis and had statistically significant lesser incidence of apnoea, PDA, thrombocytopenia, platelet transfusion, Packed Red Cells transfusion and shorter duration of CPAP ventilation. In the ELGAN (extremely low gestational age newborn) the amount of calories, proteins and fat received by neonates without ROP was higher than in neonates with ROP. In addition, the increased severity of ROP was also seen in lower gestational age infants [17]. This study shows that there is a relation between the amount of various nutritional supplements received and better weight gain in the preterm infants.

Among all the infants with ROP in this study only two were treated by laser photocoagulation without any sequel. ROP regressed in all the infants following treatment. Studies done with similar profile of infants screened for ROP in other centres from India reported incidence of ROP 11.9% and 22.3% with a good outcome using laser photocoagulation. [10,11]

In another study done by Chaudhari et al. with similar profile of infants, found septicemia, apnea, oxygen therapy, ventilation, blood products use, as a significant risk factors in univariate analysis [11]. Independent risk factors for ROP were identified by studying all risk factors with significance ($p<0.05$) using binary logistic regression. In univariate analysis PDA and birth weight were significant risk factors, while not in multivariate analysis. This may be due to lesser subjects in this group. Cumulative weight gain was the sole independent risk factors for severe ROP with 95% confidence interval ($P<0.001$).

5. Conclusion

We would like to conclude that there is a positive correlation between serum IGF-I levels and the longitudinal postnatal weight gain pattern of preterm infants. Parameters including apnoea incidence, PDA incidence, thrombocytopenia, platelet transfusion, packed red cells transfusion, mean period of gestation and mean period of CPAP were found to be statistically significant ($p<0.05$) for their association with ROP incidence. Cumulative weight gain was the only independent risk factors for severe ROP. While, surfactant requirement, culture proven sepsis, antibiotic ≥ 7 Days and mean period of supplemental O_2 (hours) were not statistically significant to be considered as risk factors for ROP. Mean serum IGF-1 levels of the two cohorts signified that the cohort without ROP had better serum IGF-1 levels as compared to the cohort with ROP. Hence, promotion of weight gain and postnatal growth by optimal nutritional supplementation might improve the condition in infants and further prevent the development of proliferative ROP.

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