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Impact of Early Postnatal Weight Gain on Retinopathy of Prematurity

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ABSTRACT
To study the impact of early postnatal weight gain on the development of retinopathy of prematurity (ROP) and need for ROP treatment. Prospective observational study of premature infants who underwent ROP Screening SNCU in Himachal Pradesh, India between August 2021 and July 2022. The average birth weight (BW) of 122 babies was 1803.87 g (range: 950-4500), with gestation (GA) 34 weeks (range: 28-40). Fifty-six infants weighed less than 1500 g, 5 were <1000 g. Two infants treated for Type 1 ROP weighed > 2 kg. Mean weight loss by day 7 was 2.6% of BW (range: -23.3 to + 35). By day 14 weight gain of 2.1% of BW (range: -27 to 43), further gained 7% of BW (range: -22 to +50) by day 21 and 11% of BW (range: -20 to +58) by day 28 of life. The ROC curve revealed discharge weight in infants had the highest association of developing ROP (Area under curve 0.708). We also observed that with increase in gestation, chances to develop treatable ROP decrease. Type 1 ROP was present in 2/4 (50%) below 28^{+6} weeks, 3/11(27%) between 29 and 30^{+6} weeks, 25/48(52%) between 31-33^{+6} weeks and 9/59 (15.2%) among infants with gestation >34 weeks. Lower GA and poor weight gain at discharge are significantly associated with the need for treatment in infants with ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease affecting premature infants[1,2]. In the western world, the reported incidence of ROP ranges from 21-65.8%[3,4], whereas in India, it varies from 38-51.9% among low birth weight babies[2]. With better survival of premature infants in SNCU, its incidence is increasing. Exact aetiology of ROP is not known, the degree of prematurity is the most consistent risk factor. The lower the birth weight and the gestational age the higher is the risk for ROP. Low postnatal weight gain is a known surrogate indicator of Insulin like growth factor-1 (IGF-1) and low IGF-1 reduces retinal vascular endothelial growth factor and increases ROP[5]. Short-term postnatal weight changes have been used to develop screening algorithms for the early detection of severe ROP in preterm infants based on GA, BW and weekly weight measurements[6]. The present study was aimed to determine the association between postnatal weight gain and development of sight threatening ROP among 'at risk' infants.

MATERIALS AND METHODS

This prospective study was carried out at newborn unit in tertiary care hospital between August 2021 to July 2022. Our twenty beds newborn unit has facility to resuscitate, provide surfactant, respiratory support and assisted ventilation. The target oxygen saturation was kept between 90-95% to avoid hyperoxia. Prior ethical approval for study was obtained and infants who met the inclusion criteria within the study period were enrolled after written informed consent given by parents/guardians of babies. No formal sample size calculation was done. Infants born in the study institute were termed inborn and those born elsewhere and referred to our hospital for treatment were termed outborn. Treatment protocols of National neonatology forum are followed in our unit and ROP screening criteria of the National Health Mission (NHM) Government of India are followed[7,8]. Timing of first eye examination was based on gestational age at birth and follow-up examinations were based on retinal findings. Those who died or were transferred out before ROP screening, major congenital malformations, chromosomal disorders, inherited metabolic diseases or parental refusal to participate in study were excluded. Clinical and demographic data was collected from patient`s medical records. Weight was taken at the time of first contact with the baby. Serial weight measurements were taken on specified days on well calibrated electronic infant weighing machine with an accuracy of ±5 g. All enrolled patients were followed up even after discharge from the SNCU, end point was until treatable stage of ROP was reached, or spontaneous regression and/or completion of vascularization. The international classification of retinopathy of prematurity was used for disease staging[7,9]. ROP was distinguished between severe ROP (or type 1 ROP) and Type 2 ROP.

Statistical analysis: Weight change between each consecutive time point from first contact to day 28 of life was calculated. Data was described in terms of range, Mean±standard deviation (SD), frequencies (number of cases) and relative frequencies (percentages), as appropriate. Chi-square and t tests were used to compare infants with ROP (Type 1 and 2) and no ROP for categorical and continuous variables, respectively. Receiver operator characteristic (ROC) curve was plotted and the criterion value was estimated depending on the specificity and sensitivity. Area under the curve (AUC) was measured. Data was analyzed with IBM SPSS 23 (SPSS, Chicago, Illinois, USA). A probability value (p-value) less than 0.05 was considered statistically significant.

RESULTS

In our study, the relationship between postnatal weight and development of ROP was determined. Out of total 154 eligible infants screened, 122 babies were included in the study (Fig. 1). There were 67 (55%) males, 88 (72%) were inborn and 21 (17%) were twins. At time of discharge, 48 (39%) had no ROP, 14 (12%) underwent Laser for type 1 ROP and 60 (49%) were diagnosed with type 2 ROP. Total 35 patients had spontaneous regression. All patients were followed up till end point of study. Outcome summarized in (Table 1). None of the infants progressed to stages 4 or 5.

The average birth weight of 122 babies was 1803.87 g (range: 950-4500 g, SD 60 g). The average gestational age was 34 weeks (range: 28-40 weeks, SD 3.08 weeks). Fifty-six (45.9%) weighed less than 1500 g, among them 5 were less than 1000 g. Two infants treated for type 1 ROP weighed more than 2 kg, one had AROP.

Table 1: Baseline characteristics and outcome of infants

Characteristics	No	Percentage
Inborn	88	72.1
Outborn	34	27.9
Multiple destation		
No	101	82.8
Yes	21	17.2
ROP status at discharge		
Type 1 ROP	14	11.5
Type 2 ROP (followed-up)	60	49.2
No	48	39.3
Type 1 ROP (laser treatment as final outcome) N = 39		
AROP, zone 1	6	15.4
AROP, posterior zone 2	16	41
Zone 2, stage 2, plus disease	11	28.2
Zone 2, stage 3, plus disease	6	15.4

Spontaneous regression (during follow-up) N = 35

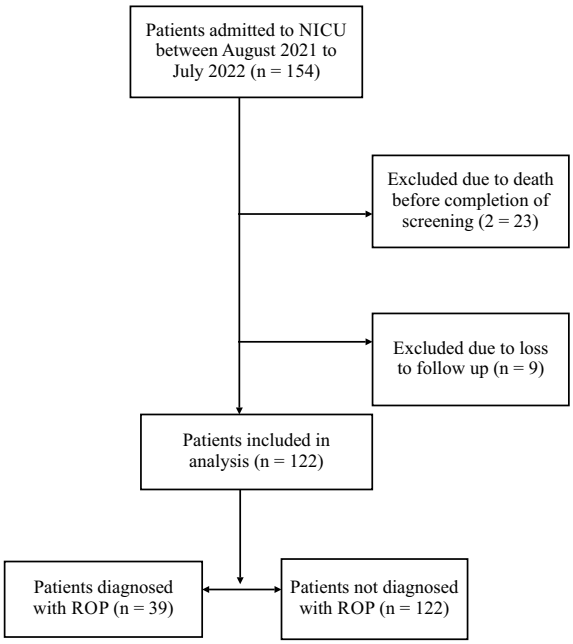

Fig. 1: Study flow

Table 2: Birth weight, discharge weight with weight gain during follow up

	At discharge		At follow up	
Weight in grams (SD)	Type 1 ROP[$]	No ROP	Type 1 ROP[#]	No ROP
Birth weight	1453.3 (50.9)	1896.57 (72.3)	1489.2 (45.3)	1949.1 (81.1)
Discharge weight	1549.6 (57.7)	2079.4 (63.1)	1685 (47.7)	2214.43 (71.2)
Total Weight gain at discharge	96.3 (32.7)	182.8 (19.3)	195.7 (26.7)	265.3 (20.5)
Weight gain at discharge (%)	6.6 (2.5)	9.2 (1.3)	13.2 (1.8)	13.6 (1.4)
Weight on day 7	1418.3 (51.4)	1826.6 (66.5)	1446.8 (44)	1877.1 (74.4)
Total weight loss day 7	35 (21.6)	70 (13.3)	42 (16.6)	72 (15)
Weight loss on day 7 (%)	-2.4	-3.7	-2.8	-3.6
Weight on day 14	1510.6 (54.4)	1998.5 (66.5)	1532.43 (44.2)	2248.9 (74.6)
Total weight gain day 14	57.3 (23.5)	101.93 (14.9)	43.2 (19.3)	299.8
Weight gain on day 14 (%)	3.9 (1.8)	5.3 (0.8)	2.9 (1.3)	15.3 (1.5)
Weight on day 21	1582 (57.4)	2181.3 (66.7)	1621.2 (48)	2425.4 (75)
Total weight gain day 21	128.7 (25.7)	284.7 (14.9)	132 (20.5)	476.3 (16.1)
Weight gain on day 21 (%)	9.1 (2)	15 (1.2)	9.2 (1.4)	24.4 (3.1)
Weight on day 28	1654 (61.8)	2245.3 (67.2)	1693.3 (50)	2588.1 (75.6)
Total weight gain day 28	200.7 (28.3)	348.7 (15.5)	204.1 (22.9)	639 (16.6)
Weight gain on day 28 (%)	14 (2.1)	18.4 (1.6)	14.1 (1.6)	32.6 (1.2)

[$]Type 1 ROP who were treated with laser prior to discharge, also include AROP and [#]Type 1 ROP who were treated with laser during entire study period, also include AROP

We observed that as GA increases, chances to develop treatable ROP decrease. Type 1 ROP was present in 2/4 (50%) below 28^{+6} weeks, 3/11 (27.2%) between 29 and 30^{+6} weeks, 25/48 (52%) between 31-33^{+6} weeks and 9/59 (15.2%) among infants with gestation>34 weeks, including one born term. Higher incidence in babies between 31-33^{+6} weeks could be because these babies had sicker neonatal period.

Expressed breastmilk feeding through orogastric tube was started in 84% neonates on day of admission, remaining 19 were fed via spoon or direct breastfed. It took 11.6 days (SD 8.6, range 1-23) for infants to reach full feeding.

Weight loss/gain during hospital stay documented in (Table: 2). Average weight loss percentage by day 7 of hospital stay was 2.6% of birth weight (BW) (SD 7%, range -23.3% to +35%). By day 14 weight gain of 2.1% of BW (SD 8.8%, range -27% to 43%), further gained 7% of BW (SD 9%, range -22% to +50%) by day 21, 11% of BW (SD 11.1%, range -20% to +58%) by day 28, 14.5% of BW (SD 11.9%, range -18%to +63%) by day 35 of life.

We determined the accuracy of rate of weight gain in predicting ROP by plotting the ROC curve. Sensitivity was plotted on the y axis and (1-specificity) was plotted on the x axis. Sensitivity and specificity were obtained for continuous score values by using cutoff points.

From the ROC curve, it was observed that discharge weight in infants had the highest chance of developing ROP (Area under curve (AUC) for ROP 0.708, 95% confidence interval: 0.633-0.837, p = 0.001) (Fig. 2a). Similarly, other ROC curves plotted to determine the accuracy of rate of weight gain in predicting treatable ROP (Fig. 2b-d).

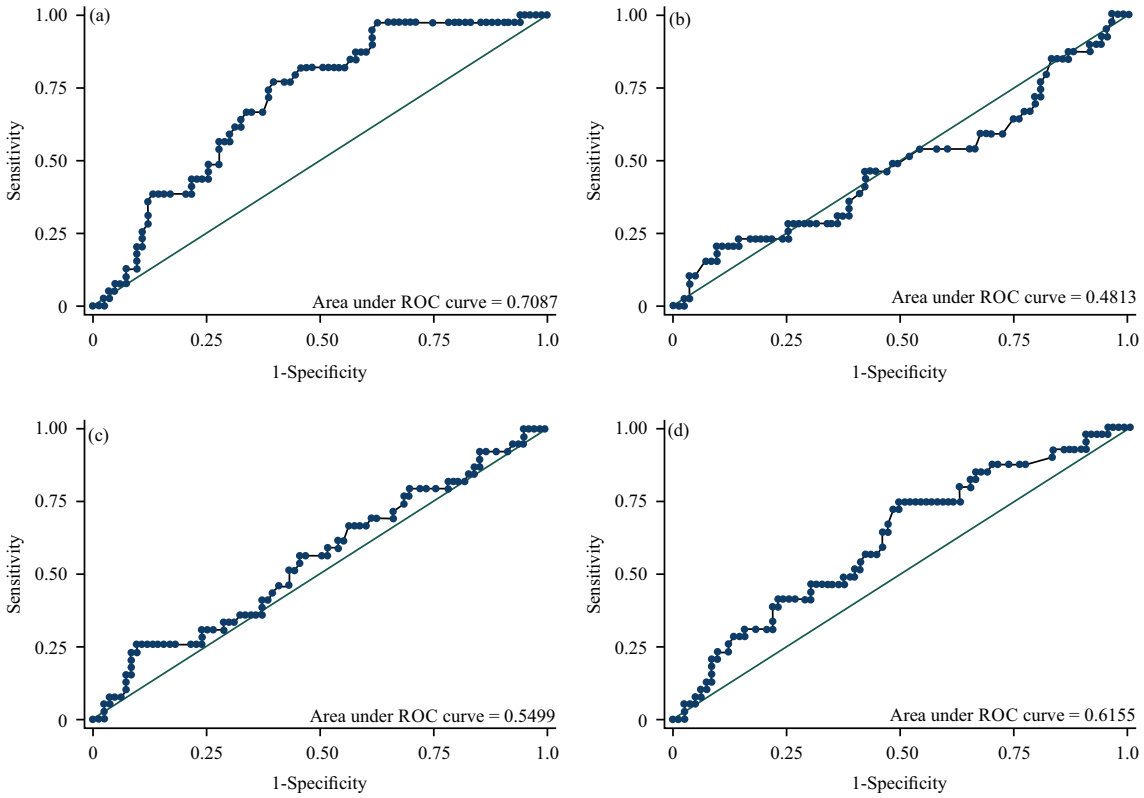

Fig. 2(a-d): ROC curves comparing changes in discharge weight, weight gain at day 7, 14 and 28 to birth weight with ROP incidence (a) Discharge weight, (b) Day 7 weight, (c) Day 14 weight, (d) Day 21 weight

In our study, upon regression analysis various other risk factors implicated in development of ROP were lower birth weight <1500 g, gestation less than 32 weeks, requirement of oxygen for more than 48 hrs, with FiO2 higher than 50%, clinical sepsis, total SNCU stay more than 14 days, CPAP support with FiO2 >50% and longer time to achieve full feeds on breast milk (more than 10 days) and poor postnatal weight gain were associated with severe ROP requiring laser treatment. Treatment of apnea with caffeine along with KMC was found to reduce ROP among high-risk newborns.

DISCUSSIONS

The present study was conducted prospectively on 122 inborn/outborn newborns at risk of developing ROP, in whom the relation between the post natal weight gain and occurrence of ROP was evaluated. We observed that discharge weight of infants is an independent risk of severe ROP requiring treatment. Total 39 infants developed treatable ROP.

Normal rate of weight gain in infants is approximately 25-30 g day^{-1} for the first 3 months of life[2,5]. Failure of IGF 1 spike to occur is a common denominator between poor weight gain and ROP. Rate of weight gain, which is easily measurable, may thus act as a marker for ROP, a potentially blinding disease for the preterm infants. Our study results corroborated with the above hypothesis.

The current screening guidelines for ROP take only BW and GA into consideration[2,4]. More studies to identify correlation between poor relative and absolute postnatal weight gain as risk factors for developing ROP are required. Screening algorithms for ROP, such as WINROP and CO-ROP use poor postnatal weight gain as a predictor to identify infants at higher risk of developing ROP[6,10-12].

Clinical studies also demonstrated association of low postnatal serum IGF-1 levels and increased risk of ROP[5]. However, serum IGF-1 measurement is not routinely available in every SNCU. The use of postnatal growth is a surrogate measurement for IGF-1levels, even among the few infants who develop severe ROP but have a higher BW or older GA. ROC curves of discharge weight, weight at Day 7,14, 21 and discharge compared to birth weight with severe ROP (Fig. 1) showed discharge weight is a significant predictor for severe ROP.

India is in the middle of ROP epidemic and SNCU managing sick and preterms are having huge burden of Retinopathy of prematurity[2]. There is limited availability of ophthalmologists with ROP expertise,

thus acting as a barrier to ROP screening. The screening algorithm for ROP is already well established in the form of RBSK guidelines. Optimizing screening criteria and incorporating discharge weight and rate of weight gain of a preterm can help us to mark high priority babies, especially when the GA is unknown. This will also help to reduce the number of ROP screenings, as they are expensive and time consuming for parents and ophthalmologists, expensive and painful for the infants. This may be a step to prevent avoidable childhood blindness in the society.

Strength of our study was its prospective nature and all the cases were closely followed up and treated. Our study has consistency as all cases were evaluated and managed by a single clinician. Weight was measured on specific decided intervals. We also checked the association of other risk factors with ROP. Limitations of our study include small sample size. We did not calculate weight gain on daily basis during admission and discharge.

CONCLUSION

We inferred from our study that post natal weight gain has a promising role in prediction of ROP. Rather than replacing the present guidelines, weight gain can be meticulously used as a triage to focus on infants with lesser weight gain who are at risk of developing severe ROP. Nation based prospective studies are warranted to corroborate our results and test the generalization of our current findings in different populations.

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