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Research Article

Impact of Early Nutrition on Postnatal Growth and Neurodevelopmental Outcome in Very Low Birth Weight Infants in a Tertiary Care NICU in India

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Received: September 07, 2021; **Published:** September 22, 2021

Abstract

Background: Postnatal growth restriction has become a major concern as survival rate of extremely low birth weight infants increased. In developing countries many of these infants are born growth restricted compounding to extrauterine growth restriction. Our aim was to study the impact of early nutrition on post-natal growth and short-term neurodevelopmental outcome of infants born under 34 weeks gestation.

Methods: In this retrospective study, we analyzed the caloric and protein intake during the first 14 days of life in preterm infants under 34 weeks GA (n = 37) and their relation to extrauterine growth restriction (EUGR). We developed a new EUGR growth curve and classified infants into mild, moderate, and severe EUGR. Mean BW and GA were 1380 ± 349 grams and 31 ± 2.62 weeks, respectively. Neurodevelopmental assessments were performed at 18 months corrected postnatal age.

Results: The incidence of EUGR was 100% in this cohort based on Olsen growth curve and 86% in the Fenton growth curve. Moderate to severe EUGR group had lower BW, received less calories during the first 14 days of age, had longer hospital stay, and worse neurodevelopmental outcome at 18 months compared to mild EUGR group. There were no differences in gestational age at birth, protein intake, incidence of sepsis or RDS between the groups.

Conclusion: In this single center study we found that nutrition during the first 2 weeks of postnatal age has direct effect on the incidence of EUGR and impacts long-term outcome of preterm infants.

Keywords: *Child; Intestinal Parasitism; Giardia lamblia; Treatment*

Abbreviations

BW: Birthweight; BPD: Bronchopulmonary Dysplasia; ELBW: Extremely Low Birthweight; EBM: Expressed Breast Milk; EUGR: Extrauterine Growth Restriction; GA: Gestational Age; HM: Human Milk; HMF: Human Milk Fortifier; IVH: Intraventricular Hemorrhage; LBW: Low Birthweight; NEC: Necrotizing Enterocolitis; OFC: Occipitofrontal Circumference; PDA: Patent Ductus Arteriosus; PCA: Post Conceptional Age; PVL: Periventricular Leukomalacia; RDS: Respiratory Distress Syndrome; ROP: Retinopathy Of Prematurity; SGA: Small For Gestational Age; VLBW: Very Low Birthweight

What is Known

Surviving extremely low birth weight infants have significant growth failure postnatally. Higher nutritional intake has not been able to correct this phenomenon and has long term sequelae.

What is New

In this study we have identified that the first two weeks of postnatal nutrition contributes to this growth failure significantly. Focusing on early nutrition during the first two weeks after birth can potentially ameliorate this problem.

Introduction

Postnatal growth restriction of varying degrees is prevalent in ELBW infants, particularly in the sickest infants [1-4]. Although non-nutritional factors may contribute to the development of growth failure, delays in regaining birth weight and low nutrient intakes play a major role. Compared with fetal nutrient intakes, the early parenteral and enteral nutritional support of ELBW infants results in substantial protein and energy deficits that persist postnatally and can be responsible for subsequent postnatal growth restriction [3,4].

Previous studies have reported that ELBW (< 750g) infants often remain physically smaller than term-born infants during infancy and childhood. Suboptimal neurodevelopmental outcomes are more common in infants with growth failure particularly in those with subnormal postnatal head growth [1,3,5,6]. Malnutrition at a vulnerable period of brain development has been shown to result in decreased number of brain cells as well as deficits in behavior, learning, and memory [7-9].

Nutritional deficiency during pregnancy, incidence of low birth weight and fetal growth restriction are common in India. We have noticed that almost all infants are fed exclusively breast milk and yet preterm infants have sub-optimal postnatal growth. Since most of these infants are on full enteral feeds (150 to 180 ml/kg/day) by 2 weeks of age, the impact of early nutrition (≤ 2 week of postnatal age) on postnatal growth failure is not known.

We hypothesized that early nutrition (≤ 2 week of postnatal age) has direct correlation to EUGR and will adversely affect neurodevelopmental outcome as measured by MDI/PDI in preterm infants.

Materials and Methods

This is a retrospective study of the data collected from the medical records of infants admitted to our tertiary care NICU during a period of 24 months (12/2010 to 11/2011). The study was approved by the institutional research ethics committee. All babies < 34 weeks gestation or birthweight < 1900 gms were included in this study. Infants with perinatal asphyxia, chromosomal or major congenital anomalies, symmetric SGA infants, out born babies > 5 days of age at the time of admission, and infants who had meningitis were excluded from the study as it may impact neurodevelopment. The following data were obtained from the medical records. Demographic data: BW, GA, APGAR scores at 1 and 5 minutes, OFC, daily weights, weekly OFC, nutrient intakes, time to full feeds and length of stay. Nutrient intakes (calories and protein/kg/day) during the initial 14 days of postnatal age were calculated on day-to-day basis. Incidence of late onset sepsis, RDS, BPD, NEC, hemodynamically significant PDA requiring medical or surgical treatment were also recorded.

Gestational age was calculated from the obstetric records (from last menstrual period dates and early ultrasound done before 8 weeks of gestation). If this not available gestational age was determined by physical examination [10]. BPD was defined as requirement for supplemental oxygen at 36 weeks of postconceptional age (PCA). Intrauterine growth curve described by Olsen., *et al*. and Fenton., *et al*. were used to estimate the centile at birth and to define EUGR postnatally [11,18]. Small for gestational age (SGA) was defined as birthweight < 10^{th} percentile. Motor Developmental Index (MDI) and Psychomotor developmental index (PDI) were assessed with DASII (Developmental Assessment Scale for Indian Infants – Modified Bayley) at a mean corrected age of 17.5 ± 1.6 months [20]. Individuals performing the developmental assessments were neither aware of this study nor the postnatal growth classification of the infants.

During the study period, all infants received intravenous 10% dextrose infusion on the first day at a rate of 5.5 - 8 mg/kg/minute along with parenteral amino acids (Aminoven 10%, Frasenius Kabi) 2 - 3 g/kg/day which were increased to a maximum of 4 gm/kg/day by the

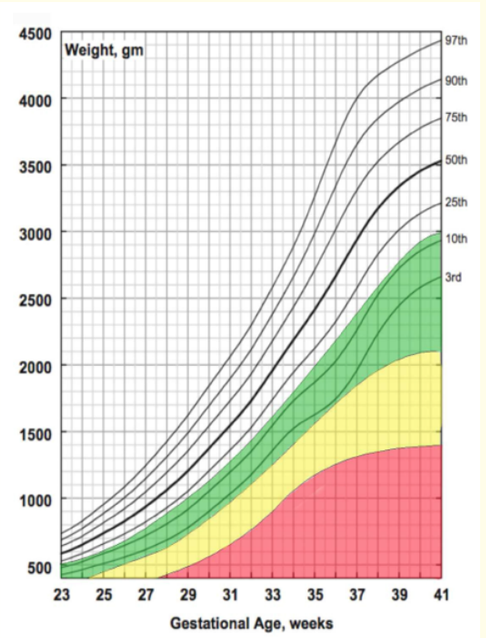
4th day of life as per the unit's guidelines for LBW infants. Intravenous lipid infusion (Omegaven 10%, Frasenius Kabi) was administered at 0.5 gm/kg/day and increased to a maximum of 3.5 gm/kg/day at the discretion of the treating physician. Intravenous dextrose concentration was gradually increased to a maximum intake of 13 mg/kg/minute if tolerated over subsequent days. The nutritional goal in our unit was to provide 80 kcal/kg/day by day 3 - 4 of life and 120 kcal/kg/day by day 7 of life. Electrolytes were monitored at 24 hrs of age for all infants on parenteral nutrition, subsequent monitoring were done based on the clinical discretion of the treating physician. Serum electrolytes were monitored (q 12h for first 72 hours) more frequently in ELBW infants. Liver and renal functions were monitored based on the clinical condition of the infant. Infants receiving exclusive parenteral nutrition had total parenteral nutrition panel: (electrolytes, BUN, Creatinine, Calcium, Phosphorus, Alkaline Phosphatase, total and conjugated bilirubin, Liver function tests) monitored weekly. Parenteral nutrition complemented enteral nutrition if nutritional goals were not achieved on enteral nutrition alone.

Insulin was not administered unless blood glucose levels exceeded 250 mg/dL despite reduction of intravenous dextrose to 5.0 to 5.5 mg/kg/min. The initiation of enteral feeding was at the discretion of the neonatologist but almost all infants (95%) received expressed maternal milk (HM) within 24 to 36 hours after birth. Infants were started on enteral feeds at 20 ml/kg/day at 3 hourly intervals and increased by 20 ml/kg/day every day until they are on 120 ml/kg/day when the parenteral nutrition is discontinued which was our feeding protocol. When HM was not available, premature infant formula (Dexolac Special Care, Nutricia) was used. Fortification of HM was started when infants tolerated enteral feed volume of 80 - 100 ml/kg/day. (Lactodex HMF, Raptakos Brett and Co. LTD) (1 sachet was added to 50 ml of EBM) HMF was used in all preterm infants to enhance enteral nutrition. Energy and protein contents of fortified milk were calculated according to the manufacturer's label.

Weight was measured daily on an electronic scale (± 5g); weight changes (g/kg/day) were calculated during hospital stay until discharge. OFC (cm) was measured over the largest occipital-frontal area with a paper tape. Energy (kcal/kg/day) and protein intakes (g/kg/day) from parenteral and enteral sources were calculated daily and the cumulative intake over first 2 weeks were also calculated.

We defined EUGR as weight < 80% of the 50th percentile of the intrauterine growth curve for corrected gest age at discharge [11,13,18]. In this study EUGR is defined by body weight below the 10th percentile of the expected intrauterine growth at 36 week PCA or at discharge. This corresponds to 80% of the 50th centile for age. We further classified EUGR into mild, moderate, and severe.

For example, if an infant is discharged at 35 weeks PCA (gestational age at birth + postnatal age) and the 50th percentile of the weight for that age is 2400 gms, then 80% of that weight would be 1920 gms. Thus, infants under 1920 gms at 35 weeks postmenstrual will be classified as EUGR. Actually, this falls between 3rd and 10th percentile of the normal growth curve. We classified EUGR further as mild (60 - 79%), moderate (40 - 59%) and severe (< 40%). These are shown in figure 1.



Grades of EUGR		
	Mild EUGR	60 - 79%
	Moderate EUGR	40 - 59%
	Severe EUGR	< 40%

Figure 1: *Based on reference 11.*

Results

Thirty-seven infants were included in this study. Mean BW and GA were 1380 ± 349 gms and 31 ± 2.62 weeks, respectively. Demographic details of the infants are summarized in table 1 and 2.

BW. gms (mean ± sd)	1380 ± 349 (range: 712-1936)
GA. weeks (mean ± sd)	31 ± 2.62 (range: 27-32)
AGA:SGA (Olsen growth curve): n (%)	26:11 (69:31%)
AGA:SGA (Fenton growth curve): n (%)	31:6 (83.8:16.2%)
Length of stay (days)	31.78 ± 23
Gestational age at discharge (weeks)	35.3 ± 2

Table 1: *Demographic data (n: 37).*
BW: (1500-1999 gms) n=17; (1000-1499 gms) n=12; (500-999 gms) n=8.

	Mild (N:22)	Moderate/Severe (N:15)	P Value
GA (wks)	31.45 ± 2.11	30.33 ± 3.19	0.25
BW (gms)	1550.09 ± 272.77	1131 ± 298.66	0.00016
SGA	3	9	0.005
Calorie (Kcal/kg/d)	86.82	64.79	0.03
Protein (gms/kg/d)	2.79 ± 0.22	2.86 ± 0.13	0.27
MDI:	90 ± 22.8	62.9 ± 30.96	0.048
PDI	112.2 ± 6.76	69.55 ± 34.73	0.003
Surfactant	13 (35%)	12 (32%)	0.28
Sepsis	6	7	0.3
Length of stay (d)	22.13 ± 14.78	45.93 ± 25.93	0.001
Discharge PCA (wks)	34.45 ± 1.01	36.53 ± 2.58	0.001

Table 2: *Differences between mild to moderate/severe EUGR.*

Regardless of the growth curve used (Fenton vs Olsen) [11,18], 86 to 100% of infants had varying degrees of EUGR. The EUGR infants were further classified as mild (n = 22 (60%)), moderate (n = 13 (35%)) and severe (n = 2 (5%)). For statistical analysis moderate and severe EUGR infants were combined into a group (moderate/severe EUGR group) and compared with the infants who developed mild or no EUGR. The incidence of SGA (at birth) was 31% (n = 12), infants who developed moderate to severe EUGR had significantly lower birth weights (1131 ± 298.66 gms) and were more likely to be SGA at birth. None of the SGA infants were symmetric SGA. Twenty-five infants (67.5%) developed RDS requiring surfactant therapy.

Developmental assessment was performed on 19 infants from this cohort at a mean postnatal age of 17.5 ± 1.6 months (corrected age). MDI and PDI were significantly lower in the severe and moderate EUGR vs mild EUGR (p = 0.05). There was significant negative correlation of caloric intake to severity of EUGR (p = 0.006). Lower MDI and PDI were significantly correlated to severity of EUGR and lower caloric intake. There were no correlations between protein intake, BW, GA, discharge weight, sepsis, or length of stay (LOS) to MDI and PDI.

Post discharge weight gain had no impact on MDI and PDI. There were 13 (35%) babies who developed sepsis (early onset sepsis=2; late onset sepsis=11). Infants who received fewer calories during the first 2 weeks also had higher incidence of sepsis (p = 0.01).

Discussion

EUGR is a recognized problem in ELBW infants, although the growth curves and the methodology used to detect EUGR have not been standardized [18,19]. In this study we developed a color-coded growth chart to subclassify EUGR into mild, moderate, and severe forms of EUGR as shown in figure 1. This was based on the growth curve published by Olsen., *et al*. from a sample size of 130,111 infants of which 11, 311 infants were under 30 weeks gestation [11]. We compared this growth curve with the growth curve published by Fenton., *et al*. which was based on meta-analysis of several studies [18]. Utilizing either this growth curve did not change the results of our study significantly. We feel that a color coded growth curve depicting mild (green), moderate (yellow) and red (severe) will assist the caregivers in determining the severity of EUGR and to identify at risk infants for adverse neurodevelopmental outcome, giving them an opportunity to enroll these infants in early intervention programs.

Previous studies have shown than EUGR is common in VLBW and ELBW infants, regardless of growth status at birth [1,12,13]. In this cohort, using Olsen' growth curve, 11 infants (31%) were SGA at birth and 8 of those infants (75%) developed severe EUGR and the rest developed mild EUGR. SGA babies constituted 13.6% of the mild EUGR and 60% of the severe EUGR groups. Utilising Fenton's growth curve, there were 6 infants in the SGA group and all of them developed severe EUGR. The differences in results between Fenton or Olsen growth curves were not statistically significant. During the first 2 weeks of postnatal life there was significantly lower caloric intake in infants who developed moderate to severe EUGR. The reasons for lower caloric intakes were multifactorial and might be related to co-morbidities such as respiratory distress, sepsis, PDA requiring fluid restriction, feeding intolerance etc. There was no difference in the protein intake during the same period between the two groups. As intralipids are expensive in a developing country like India, it was sparingly used in the parenteral nutrition.

There are many postnatal factors that can predispose an infant to EUGR. These include BPD, sepsis, severe NEC, short gut syndrome, severe intrauterine growth restriction particularly symmetric IUGR, post-surgical states, delayed enteral feedings, and extreme prematurity [12,13]. In our study there were no cases of BPD or NEC. A significant factor for EUGR was the nutrition during the first two weeks of postnatal age and the extreme prematurity. Severity of the EUGR was inversely proportional to the birthweight. All subjects in this study were on full enteral feedings (breast milk with human milk fortifier) within 12 - 14 days. Still, EUGR was quite common in all these infants. This study shows that caloric intake during the first 14 days of life is an important factor that leads to severe EUGR. Protein intake specifically was not a significant factor in the genesis of EUGR. The incidence of late-onset sepsis was 35% and probably contributed to nutritional inadequacy, but we did not find incidences of sepsis or RDS (requiring surfactant therapy) as factors leading to severe EUGR. Postnatal growth of the of ELBW infants in the NICU has been reported to have a direct relation to subsequent neurodevelopment [19]. Although developmental assessments were performed in only 52% of the cohort, the MDI and PDI were significantly lower in moderate to severe EUGR group. Whether the adverse neurodevelopmental outcome in this group was due to inadequate caloric intake during the first 2 weeks of postnatal life is unknown. We speculate that there is a critical period soon after birth where nutritional deficiency has long-lasting effects in brain and other vital organ development. Inadequate nutrition during this period may affect the hyperplastic phase of growth resulting in fewer number of cells in organs including the brain. Besides epigenetic factors from nutritional deficiency can affect imprinting in the brain which can have long-lasting effects in development [21]. We realize that only 52% of enrolled infants had the neurodevelopmental assessments in this study. Ideally, 80% or higher longitudinal follow-up data would be required for firmer conclusions. Currently, we are planning to recruit a larger number of infants from this cohort to assess their cognitive and higher executive functional skills at 5 - 7 years of age.

If return to prenatal growth trajectories is a goal, infants must receive sufficient calories and protein to support weight gains that exceed in utero rates (> 15 g/kg/day), an uncommon event in our study groups. Ziegler suggests that fixed protein intakes, such as those provided by commercial formulas and fortified human milk (especially beyond the early weeks), are inadequate for addressing growth

needs of the premature infant [14]. He speculated that selectively providing increased protein for the small premature infant may better meet their needs.

Previous reports have indicated that improved nutrition in the early postnatal period could ameliorate morbidities that negatively impact growth in this population [15-17]. Therefore, exploring a strategy to improve nutritional support early in an infant's hospital course may, in and of itself, decrease morbidities that impair growth and outcome.

While attempting to support an infant's postnatal growth to in utero growth trajectory is a desirable goal, it is almost impossible to attain it particularly in extremely low birth weight infants. Focusing on early postnatal nutrition is extremely important and may have long term effects on outcome.

Conclusion

In this single center study we found that nutrition during the first 2 weeks of postnatal age has direct effect on the incidence of EUGR and impacts long-term outcome of preterm infants.

Acknowledgements

We gratefully acknowledge the developmental assessments performed by Ms. Thanuja Sasi who provided the data on MDI and PDI.

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Volume 10 Issue 10 October 2021