



First Week Protein and Energy Intake and its Effect on Growth at Hospital Discharge and at Term Gestation in Very Preterm Infants on Exclusive Human Milk Feeding

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ABSTRACT

In a unit with aggressive enteral and parenteral nutritional policy, the actual calorie and protein intakes of preterm infants are less than targeted. In this large cohort of infants with gestation <33 weeks, when aggressive TPN was the routine and enteral feeding was aggressive and with only human milk feeding, the average calorie intake and the protein intake was very much less than the recommended daily allowance.

Keywords: Nutrition; Growth; Term PMA; Infants

INTRODUCTION

Optimal nutrition in preterm infants has long lasting effects on the growth and neurocognitive outcomes. Aggressive enteral and parenteral nutrition in the first few weeks of life have resulted in better ex-utero growth and lesser extra uterine growth restriction. Although protein targets >3 g/kg/day and calorie targets >125 kcal/kg/day are the current recommendations for best nutritional management in the NICU, achieving these targets in the first week is difficult in many newborns because of fluid restrictions, metabolic disturbances, interruption of parenteral nutrition, inability to fortify enteral feeds and critical illness. The actual intakes of calories and protein in the first week after birth and their effect on the immediate growth in preterm infants are not well studied. Hence we planned this study with a primary objective 'to evaluate the effect of first week protein and energy on the growth outcomes at hospital discharge and at term gestation (PMA 37 to 40 weeks).

Study design

Prospective observational longitudinal study.

Study site

Tertiary care neonatal unit.

Primary objective

To evaluate the effect of first week protein and energy on the growth outcomes at hospital discharge and at term gestation (PMA 37 to 40 weeks).

Period of study

2 years from June 2016 to July 2018.

Place of study

Fernandez hospital, Hyderabad is a tertiary care hospital for newborn and mothers.

Inclusion criteria

All newborns with gestational age 26 0/7 to 326/7weeks (182 to 230 6/7days) admitted to the NICU within 24 hours of birth.

Exclusion criteria

- Death within 7 days of life
- Major malformations
- Transfer to another hospital before achievement of full enteral feeds or within 7 days of life

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MATERIALS AND METHODS

Gestational age was assessed on day 1 of admission in NICU. Gestational age in completed weeks was based on first trimester ultrasound or estimated from new Ballard score. All infants with gestational age between 26 0/7 to 326/7 (182 to 230 days) were enrolled. Birth weight was recorded within 10 minutes of birth. The neonate was classified as appropriate for gestational age or small for gestational age by plotting the birth weight against the best gestational age estimate on the Fenton growth charts [1]. The length and the head circumference were documented within 24 hours of birth. Data for each eligible infant was prospectively collected using described definitions for data variables and clinical conditions.

Anthropometric measurements

Body weight was recorded daily till the baby regains birth weight or till day 14 whichever occurs later. After that, it was recorded weekly till a postmenstrual gestational age of 40 weeks is reached. Measurements were performed at a standard time each day with digital electronic scales (accuracy of ± 10 g).

Length and head circumference were measured within 48 hours of birth and then weekly till a postmenstrual gestational age of 40 weeks is reached or till death or transfer. The length was

Table 1: Targets for calories and proteins.

	Minimum	Target
Calories	75 kcal/ kg/day	125 kcal/kg/day
Protein	1 gm/kg/day	3.5 to 4.5 gm/kg/day

The actual volumes (feeds + TPN + medications + other fluids), calorie intake (EBM and donor human milk assumed to have 67 Kcal/100ml+actual TPN Kcal) and protein (EBM assumed to have 1.1 g/100 ml+protein 0.8 g/100 ml of humal milk from HMF+actual TPN protein) intake were calculated on a day-to-day basis before 8 am in the morning.

Enteral feeding protocol

Feeding for oral feeds on day 1: Trophic feeds were started on day 1 if there is no asphyxia (5 min Apgar $<$ 5) and no absent or reversal of doppler flows in the antenatal umbilical artery. In infants with asphyxia and abnormal antenatal dopplers feeds were started after 24 to 48 hours of life.

Order of choice of milk

- Mothers own milk
- Donor human milk

Method of feeding

- Tube feeds for preterm infants with gestation less than 30 weeks
- Cup and spoon or Palada feeds for neonates with gestation between 30 to 33 weeks
- Direct breast feeds for neonates with gestation greater than or equal to 34 weeks

recorded with an infantometer to the nearest 0.1 cm with the baby supine, knees fully extended and soles of feet held firmly against the footboard and head touching the fixed board. The head circumference was measured at the maximum circumference of the head (i.e., occipito-frontal) with a non-stretchable tape to the nearest 0.1 cm. Anthropometric measurements data was performed by a trained research student.

Nutrition protocol

Nutritional and fluid management of all enrolled infants was guided by a nutritional protocol elaborating on both parenteral nutrition and enteral nutrition. The ideal daily caloric and protein intake were targeted. The preferred choice for enteral feeding was mother's preterm breast milk. Donor human milk was used when mothers own milk was insufficient. All newborns on full enteral feeds (>150 ml/kg/day) were started on human milk fortifier. HMF was continued as long as the newborn was on expressed breast milk. Mothers were advised to use formula after discharge if own mothers milk was insufficient. The daily fluid, calorie and protein intake of the enrolled infants was collected prospectively from birth till completion of first week. Any deviation from the nutrition protocol was noted, the infants however would continue in the study.

Trophic feeds: Enteral feeds of 5 ml/kg/day-10 ml/kg/day and preferably colostrum.

Enteral feeds were withheld if the neonate was hemodynamically unstable, had abdominal distension (increase in girth by 2 cms), feed intolerance (altered aspirates, more than 50% feed residuals) and persistent vomiting. Kangaroo Mother Care (KMC) and non-nutritive sucking were encouraged in all infants as early as possible and as long as possible till hospital discharge.

Total Parenteral Nutrition (TPN)

All infants with birth weight less than 1250 grams and sick infants with birth weight between 1250 grams and 1500 grams, were started on intravenous fluids and parenteral nutrition [2]. Intravenous fluids were initiated with 10% dextrose and 10% aminoven (20 ml to each 80 ml of 10% dextrose) on day 1 at 60 ml/kg to 80 ml/kg. For all Very Low Birth Infants (VLBW), proteins at 3 g/kg from day 2 and lipids at 3 gm/kg from day 2 were initiated. Proteins were increased to a maximum of 3.5 g/kg to 4.5 g/kg and lipids to 3.5 g/kg to 4 g/kg. TPN was withheld if the fluids being restrictive are unable to maintain normoglycemia. As enteral intake increased, proteins were tapered to ensure that the infant gets no more than a total 4.5 g/kg/day enteral and parenteral proteins in total. Once the infant reached 100 ml/kg/d of enteral intake, proteins and lipids were stopped abruptly.

Follow up

All the discharged enrolled infants were followed up in the high risk follow up clinic weekly till the infant reached a postmenstrual gestational age of 37 to 40 weeks. Research student and trained nurses took the anthropometric measurements (weight, length and head circumference). Follow up visits were coordinated with reminder phone calls before scheduled visits. There was an additional reminder if a visit was missed.

Primary outcome

Effect of actual protein and calorie intake during the first week after birth on growth (weight, length and head circumference) of the infant at term (PMA 37 to 40 weeks) corrected age.

The secondary outcomes of the study included:

- The actual intakes of protein and calorie in the first week of life
- Weight, length and head circumference at 37 to 40 weeks of corrected age

Statistics

Six gestational age groups were created from 25 to 32 weeks (25 to 26 weeks, 27 to 28 weeks, 29 weeks, 30 weeks, 31 weeks and 32 weeks). The protein and calorie intake in the first week of birth is correlated with all the growth outcomes at 37 to 40 weeks of corrected age. Nutrition factors affecting growth outcomes at term corrected age are analysed in a linear regression model with growth as the dependent variable and total calorie (cal/kg/day), total protein (g/kg/day), TPN days

(proportion of the first week), birth weight and IUGR at birth independent variables.

Sample size

The data for this study is obtained from the patients recruited for another study postnatal growth for preterm infants with gestation less than 33 weeks [3]. No a-priori sample estimation done for this study.

RESULTS

During the study period a total of 398 eligible infants were admitted to the neonatal units. After excluding 76 infants (36 died in hospital, 40 infants got shifted to another hospital before complete care), 322 infants were eligible for growth assessment. The mean gestation and the mean birth weight of infants included in the study are 29.9 ± 1.7 weeks and 1294 ± 337 grams respectively. Sixty six infants (20%) had a birth weight <1000 grams. Thirty six (11%) infants were SGA at birth. Table 2 depicts the baseline data and the morbidity profile of infants enrolled in the study. The average duration of TPN days, the average time to reach full feeds and average time to regain birth weight was higher in the gestational group with lower gestation (Table 2). All infants in the study were on either fortified mothers own milk or donor human milk from tropic feeds till hospital discharge [4]. The average postmenstrual age at discharge was 33.8 ± 1.7 weeks and the average PMA at follow up was 38.5 ± 2.2 weeks. The average duration of hospitalization was 28 ± 20 days (Table 3).

Table 2: Baseline variables of infants survived till discharged.

	Total	Gest 2526	Gest 2728	Gest 29	Gest 30	Gest 31	Gest 32
Eligible number	398	32	60	81	73	71	81
Enrolled	322 (81)	18 (56)	37 (62)	64 (79)	65 (89)	64 (90)	74 (91.4)
Birth weight	1294 ± 337	911 ± 122	1030 ± 174	1128 ± 199	1247 ± 267	1425 ± 286	1591 ± 337
SGA	36 (11)	0	2 (5.4)	6 (9.4)	12 (18)	8 (12)	8 (11)
Male sex	174 (54)	12 (67)	22 (60)	40 (62.5)	38 (58.5)	28 (44)	34 (46)
C-section	207 (64)	13 (72)	26 (70)	35 (55)	40 (61)	41 (64)	52 (70)
Antenatal steroids	306 (95)	16 (89)	35 (95)	60 (94)	61 (94)	61 (95)	73 (99)
Maternal age	29.5 ± 4.5	30.2 ± 4.5	30.0 ± 5	29.3 ± 37	29.3 ± 4	29.05 ± 4.3	29.7 ± 5
Maternal PIH	207 (64)	13 (72)	26 (70)	35 (55)	40 (62)	41 (64)	52 (70)

Table 3: Morbidities during the hospital stay.

	Total	Gest 2526	Gest 2728	Gest 29	Gest 30	Gest 31	Gest 32
NEC> stage II	19 (5.9)	2 (11)	4 (11)	7 (11)	3 (4.7)	3 (4.6)	0

Sepsis	51 (16)	9 (50)	12 (32)	13 (20)	10 (15)	6 (9)	1 (1.4)
Severe IVH	1 (0.3)	1 (2.7)	0	0	0	0	0
Cystic PVL	6 (1.9)	1 (5.6)	2 (5.4)	1 (1.6)	0	1 (1.6)	1 (1.4)
BPD*	20 (6.2)	8 (44)	6 (16)	6 (9.4)	0	0	0
Hospital stay before discharge (d)	28 ± 20	70 ± 22	50 ± 18	35 ± 12	21 ± 72	17 ± 9	13 ± 7

The average intake of calories and the average intake of protein in the first week after birth was 73.13 ± 19.7 and 2.14 ± 0.58 respectively. The proportion of days on TPN in the first was 0.76 ± 0.33 and it was higher in the gestational age groups 25 to 29 weeks. The time to reach a calorie requirement of 120 kcal/kg/day and a protein intake of 3 g/kg/day was 9.4 ± 4.2 and 6.0 ± 4 day and the time to reach ad libitum spoon feeds by enteral route was 8.4 ± 5 days.

Proportion of days on TPN was the most important factor effecting weight (332 grams, 95% CI 4.3 to 660 grams), length (1.8 cm, 95% CI 0.42 to 3.2 cm) and head circumference (1.3 cm, 95% 0.26 to 2.5 cm) at term corrected age. IUGR at birth and low birth weight negatively correlated with length at term corrected age.

DISCUSSION

In this large cohort of infants with gestation <33 weeks, when aggressive TPN was the routine and enteral feeding was aggressive and with only human milk feeding, the average calorie intake and the protein intake was very much less than the recommended daily allowance [5]. The average calorie deficit and the protein deficit is likely to be around 330 Kcals and 9.5 grams respectively over the first week after birth in this cohort of newborns. Embleton and colleagues conducted a longitudinal prospective study of all infants admitted to an intensive care nursery over a six-month period with a gestational age <34 weeks and a birth weight <1,750 g who survived past the second day of

life by the end of week 1, cumulative energy deficit was 406 ± 92 kcal/kg and protein deficit was 14 ± 3 g/kg for infants ≤ 30 weeks gestation. For infants ≥ 31 weeks, energy deficit was 335 ± 86 kcal/kg and protein deficit was 12 ± 4 g/kg where as in our study protein deficit was lesser.

Interestingly protein deficits are less likely in more immature infants as these infants had received parenteral nutrition from the day of birth and continued to receive the same till the first week. Radmacher and associate conducted a four-year longitudinal retrospective chart review of 220 infants $\leq 1,000$ g and ≤ 29 weeks gestation. The study goal was to identify predictors of EUGR and to evaluate nutritional intake and subsequent growth of VLBW infants. Similar to our study infants, infants were included in the sample if they were admitted to the nursery within 24 hours of birth, alive at seven days, and not diagnosed with any major congenital anomalies. Infants who developed EUGR had significantly lower birth weight (46 percent were <750 g at birth) and were more likely to be SGA at birth. Birth weight percentile was the greatest predictor of EUGR; days of total parenteral nutrition and head circumference percentile at return to birth weight were the only independent predictors of EUGR [6]. Mean energy intake failed to reach 120 kcal/kg/day for either group during the study period, although EUGR infants consistently received less energy and protein than non-EUGR infants. These findings are very similar to the results seen in this study (Table 4).

Table 4: Growth and nutritional parameters.

	Total	Gest 2526	Gest 2728	Gest 29	Gest 30	Gest 31	Gest 32
Enrolled	322	18	37	64	65	64	74
B weight	1294 ± 337	911 ± 122	1030 ± 174	1128 ± 199	1247 ± 267	1425 ± 286	1591 ± 337
Time full feeds (days)	7.7 ± 5.5	12.7 ± 5.4	11.2 ± 5.4	9.4 ± 4.7	8.7 ± 4.8	6 ± 4.9	4.2 ± 2.7
Time birth weight (days)	12.3 ± 4.9	14.6 ± 3.9	14.2 ± 4.6	12.1 ± 5.1	12.8 ± 5	11.5 ± 4.5	11.01 ± 4.5
Avg TPN Days	7.6 ± 4.9	10.5 ± 4.5	9.8 ± 5.5	8.2 ± 5.4	7.5 ± 4.2	5.6 ± 4.5	4.9 ± 2.6
Hospital stay	28 ± 20	70 ± 22	50 ± 18	35 ± 12	27 ± 12	17 ± 9	13 ± 7

Calories first week (Cal/Kg/day)	73.13 ± 19.7	69.47 ± 14.8	68.8 ± 14.2	67.4 ± 16	68.98 ± 20.7	78.5 ± 19.3	80.1 ± 22.3
Cal 120/kg/day	9.4 ± 4.2 (n=265)	11.12 ± 4.9 (n=17)	12.13 ± 5.1 (n=32)	10.3 ± 2.7 (n=57)	9.8 ± 4.3 (n=58)	8.38 ± 4.2 (n=53)	6.48 ± 2.8 (n=48)
Time ad libitum	8.4 ± 5 (n=42)	15.0 ± 1.4 (n=1)	14.3 ± 8.9 (n=4)	11.3 ± 3.9 (n=4)	11.0 ± 8.6 (n=5)	7.6 ± 3 (n=8)	5.8 ± 3.1 (n=20)
Time 3 g/kg/day	6.0 ± 4 (n=262)	4.3 ± 1.8 (n=18)	7.6 ± 8.0 (n=35)	6.1 ± 3.7 (n=60)	5.5 ± 3.0 (n=60)	6.9 ± 3.8 (n=47)	5.2 ± 1.9 (n=42)
Protein first week (g/kg/day)	2.14 ± 0.58	2.60 ± 0.6	2.44 ± 0.48	2.26 ± 0.6	2.21 ± 0.61	2.01 ± 0.46	1.83 ± 0.47
Proportion TPN 1 week	0.76 ± 0.33	1.00 ± 0.0	0.95 ± 0.12	0.90 ± 0.24	0.89 ± 0.20	0.62 ± 0.35	0.47 ± 0.34
Dis Gestation (wks)	33.8 ± 1.7	35.8 ± 2.9	34.6 ± 2.4	33.9 ± 1.8	33.9 ± 1.8	33.09 ± 1.2	33.5 ± 0.9
Dis weight	1581 ± 223	1802 ± 312	1599 ± 314	1580 ± 177	1549 ± 276	1528 ± 139	1613 ± 241
Dis length	42.3 ± 1.8	43.6 ± 1.8	42.5 ± 2.2	42.1 ± 1.5	42.0 ± 1.5	42.0 ± 1.7	42.4 ± 2.1
Dis HC	29.6 ± 1.3	30.3 ± 1.7	29.6 ± 1.7	29.7 ± 1.1	29.4 ± 1.5	29.3 ± 0.9	29.7 ± 1.1
PMA at last assessment (wks)	38.5 ± 2.2	38.61 ± 2	39.08 ± 1.6	39 ± 1.0	38.8 ± 2.0	37.7 ± 2.8	38.2 ± 2.5
Weight at last PMA	2452 ± 593	2151 ± 489	2451 ± 420	2492 ± 528	2509 ± 566	2375 ± 687	2510 ± 662
Length at last PMA	0.81 ± 0.21	0.83 ± 0.14	0.81 ± 0.21	0.75 ± 0.36	0.79 ± 0.25	0.51 ± 0.43	0.67 ± 0.49
HC at last PMA	0.55 ± 0.27	0.61 ± 0.20	0.58 ± 0.16	0.60 ± 0.18	0.63 ± 0.16	0.46 ± 0.32	0.48 ± 0.36

The only nutritional parameter which correlated with growth at term corrected age was the proportional days on TPN during the first week after birth independent of birth weight and IUGR status [7-9]. Every one day increase in TPN would have resulted in an average of 45 grams increase in weight, 0.25 cm in length and 0.2 cm increase in head circumference at term corrected age. Study of extreme preterm 22 to 26 6/7 week study found that increasing calorie 77 to 98 kcal/kg/day and protein 2.4 to 3.6 in first postnatal week resulted in significant improvement in growth where as our study reflects that proportional increase in TPN will lead to better growth. Study of early and aggressive introduction of total parenteral nutrition and enteral feeding resulted in better growth in weight, length and head circumference, and a reduction of nutritional deficits at 40 weeks of postmenstrual age were like our study result. In a randomized controlled trial of an aggressive nutritional regimen in sick VLBW infants, showed an improvement of growth in the early neonatal period and at hospital discharge without increasing the risk of adverse clinical or metabolic sequelae which is similar to our result [10-12]. Aggressive enteral feeding with human milk is expected to result in lower growth in the follow up in spite of fortification. However human milk feeding is the gold standard and we still do not know if better growth by

parenteral nutrition will result in better long term metabolic and neuro-cognitive outcomes.

Large number of infants, aggressive parenteral and enteral nutritional nutrition, good follow up and only human milk enteral feeding are the main strengths of this study. Assumption of calorie and protein content of fortified human milk as 80 kcal/100 ml and 2 g/100 ml and inability to measure the calorie and protein content of donor milk and mother own milk during the daily feeding schedule is the limitation of this study.

CONCLUSION

In a unit with aggressive enteral and parenteral nutritional policy, the actual calorie and protein intakes of preterm infants are less than targeted. Proportion of days on parenteral nutrition during the first week after birth is the main determinant of growth at term corrected age adjusted for birth weight and IUGR status.

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CONFLICT OF INTEREST

None.

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