Original Article

# Postnatal growth and short-term complications in very low birth weight neonates receiving total parenteral nutrition

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## Abstract

**Objective:** To study the postnatal growth and short-term complications in very low birth weight preterm neonates receiving total parenteral nutrition (TPN). **Methods:** This prospective, observational study was conducted in the neonatal intensive care unit of a tertiary care hospital in South India. All neonates with birth weight <1250 g and <32 weeks of gestation who received TPN and survived at least 7 days were studied prospectively. Amino acid infusion was started at 1 g/kg/day on day 1 and graded up to 4 g/kg/day. Lipids were started on the day 2 of life at 1 g/kg/day and graded up to 3 g/kg/day. Enteral feeds were introduced within 3 days of life. TPN was stopped once enteral feeds reached 100 ml/kg/day. Postnatal growth and biochemical and hematological parameters were also monitored. **Results:** Time to reach full enteral feeds was 11.3±4.5 days, cumulative weight loss proportion (in %) was 8.5±4.7, and number of days to regain birth weight was 11.1±4.5 days. Mean growth velocity (GV) at 30 days of life and 40 weeks of postmenstrual age (PMA) was 16.37±4.8 g/kg/day and 20.03±5.8 g/day, respectively. Mean GV of appropriate for gestational age (AGA) infants was 3.13 g/kg/day, lower compared to small for GA (SGA) infants at 30 days PMA (p=0.01). However, there was no statistical difference in GV between AGA and SGA infants at 40 weeks of PMA. There was no correlation between energy intake on the day 7 and weight and head circumference at 40 weeks of PMA. Hyponatremia was observed in 40.6% infants receiving TPN, and there were no other significant complications. **Conclusion:** Conventional TPN was associated with favorable postnatal growth until 30 days of postnatal life. However, catch-up growth at 40 weeks of PMA was not satisfactory. Mean GV of AGA infants was found to be lower compared to that in SGA infants at 30 days of postnatal life. Besides hyponatremia, there was no major complication due to TPN in this study.

**Keywords:** *Postnatal growth, Short-term complications, total parenteral nutrition, very low birth weight neonates*

Very low birth weight (VLBW) infants are born at a time of otherwise rapid intra-uterine brain and body growth. These infants have very limited endogenous stores and increased metabolic demands; hence, the rapid establishment of postnatal nutrition is essential. The goal should be to provide nutrition to achieve a growth velocity (GV) similar to intra-uterine GV. Parenteral nutrition must be initiated as soon as possible in VLBW preterm infants to prevent postnatal growth failure and improve neurodevelopmental outcome [1]. The Committee on Nutrition of the American Academy of Pediatrics has recommended a caloric intake of 120 Kcal/kg/day for children enterally fed and 80-100 Kcal/kg/day for those receiving total parenteral nutrition (TPN), with a protein intake of 3.5-4 g/kg/day [2].

However, it is difficult for the most VLBW infants to reach the suggested caloric and protein intake in the first few weeks of life due to need for fluid restriction, delayed initiation of parenteral aminoacid solutions and lipids, and immaturity of intestinal functions, all of which contribute to the slow process of enteral and parenteral nutrition. Most infants gain less weight compared to fetuses of the same gestational age (GA). As a result of this growth deficit, a large proportion of such infants remain below the 10th centile for postmenstrual age (PMA), and this subnormal growth often persists into childhood with potential adverse effects on later neurodevelopment [3]. Greater weight gain before 40 weeks PMA is associated with better outcomes [3].

Thus, it remains important to understand the nutritional factors that influence growth in the early neonatal period and to identify factors that might maximize the growth. Conventional TPN is being used in almost all tertiary care neonatal intensive care units (NICUs) for preterm neonates, but there are few studies which examined the impact of conventional TPN on the early growth pattern of these neonates. Hence in this study, we examined the impact of nutritional practices on GV during the first month of life and at 40 weeks of PMA.

## METHODS

This observational study was conducted prospectively from January 2012 to August 2013 at NICU of a tertiary center in South India. We obtained approval of Institutional Ethics Committee for this study and parents' consent was taken before enrollment of subjects. Both inborn and outborn neonates with birth weight <1250 g and <32 weeks of gestation who received TPN and survived at least 7 days were included. Neonates with major congenital anomalies, syndromic features, referred after day 3 of life, critically ill and hence could not be disconnected from the ventilator for interventions like weighing were excluded from the study.

The neonates satisfying the inclusion criteria were started on intravenous (IV) Fluids and considered for TPN administration from day 1 of life. This practice was based on the guidelines that all premature neonates <35 weeks of gestation should be started on parenteral nutrition along with enteral nutrition [4]. The total fluid of 80 ml/kg/day were administered on the day 1 of life and increased daily by 20 ml/kg/day up until 150 ml/kg/day was reached. Dextrose with calcium was given on first 2 days of life, and electrolytes were added from the day 3 onward. Dextrose was started at glucose infusion rate of 6 mg/kg/min on day 1 of life and increased or decreased so that a glucometer random blood glucose levels were maintained between 60 and 120 mg/dl. Sodium was supplemented at 3-5 mEq/kg/day and potassium at 2 mEq/kg/day and titrated according to serum electrolyte levels which were done twice a week.

Parenteral nutrition included amino acids (10% aminoven) and lipids (10% intralipids), which were started at 1 g/kg/d and both were graded up every day by 1 g/kg/day up to maximum of 4 g/kg/day for amino acids and 3 g/kg/d for lipids. Parenteral nutrient admixtures were prepared under laminar flow. Amino acids and lipids were infused separately, and lipid was covered with dark paper if neonate was receiving phototherapy. The bottles along with tubings were changed every 24 h.

Biochemical and hematological parameters were monitored as the TPN was graded up. Serum electrolytes and renal function tests were done twice a week (on day 4, 7, 11…). Blood gas analysis was done on the day 4. Liver function tests (LFT), total cholesterol, triglyceride (TG), and complete blood counts were done weekly once. Lipid solution was decreased by 0.5 g/kg/day when TG was between 170 and 200 mg/dL. Intralipid was stopped when the liver enzymes were elevated more than three times normal limits and TG above 200 mg/dL. The amino acid administration was stopped when the serum creatinine was more than 95th centile for the GA.

Expressed breast milk was introduced within 3 days of life. If breast milk was not available, enteral nutrition was delayed. Feeds were graded up by 10-20 ml/kg/day as tolerated by the neonates. Feeds were interrupted when there was blood tinged or coffee ground aspirate, abdominal girth measured at the umbilicus increased by 2 cm or more from baseline in 6 h interval, reduced/absent bowel sounds, abdominal tenderness, and gastric residual volume was 50% or more. TPN was stopped once enteral feeds reached 100 ml/kg/day.

GA was estimated by antenatal ultrasonogram or last menstrual period. Detailed nutritional data included type and volume of IV solutions, the composition of parenteral nutrition, type, and volume of enteral feedings and additives. All infants were weighed unclothed using Essae DS 252 weighing scale which has an accuracy of 5 g. Weight was recorded daily until discharge and at 40 weeks of PMA. Because of the expected weight loss during the first 10 days of life, GV was calculated for the interval between days 10 and 30 by the following formula:

GV at 30 days in g/kg/day = 1000×([wt 30−wt 10]/wt 10)/(30-10). GV at 40 weeks of PMA in g/day = wt at 40 weeks PMA - wt at day 10/number of days between 40 weeks of PMA and day 10. Head circumference (HC) was recorded after 24 h of life and at 40 weeks PMA. Growth was plotted on the Fenton's fetal-infant growth chart which mimics intra-uterine growth curves. Neonatal morbidity, mortality, and laboratory details were recorded in the study proforma. Neonatal morbidity included sepsis (clinical and culture proven), intra-ventricular hemorrhage (IVH), patent ductus arteriosus (PDA), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD).

Neurosonogram was obtained on the day 3 and day 30 of life to look for IVH and PVL, respectively. Echocardiography was done at the end of the first week to rule out PDA or other cardiac anomalies. Screening for ROP was done at 32 weeks or at postnatal age of 4 weeks whichever was later.

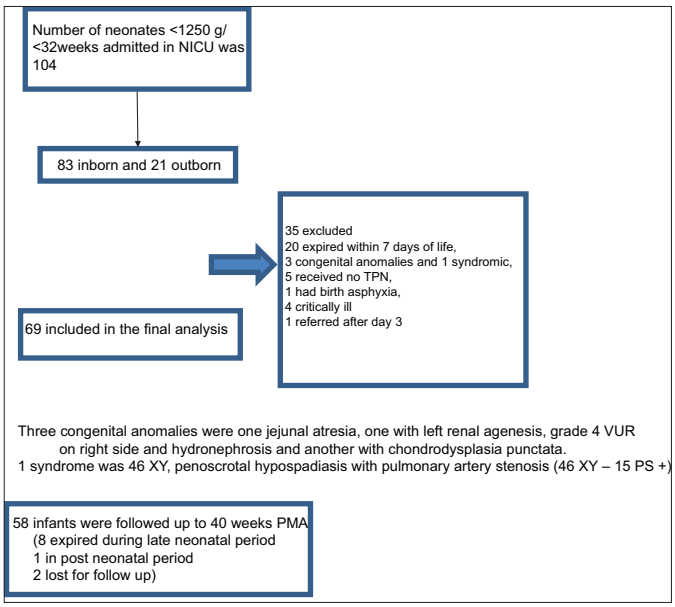
Data were analyzed using SPSS Version 16.0 Software. Categorical variables were analyzed by chi-square test. $p<0.05$ was considered as significant.

## RESULTS

Study flow diagram:

The study population included 69 preterm (<32 weeks gestation) neonates. Among them, 21 were <28 weeks, 40 between 28 and 30 weeks and 8 were >30 weeks. Neonates with birth weight <1000 g were 24 and 1000-1250 g were 45. 40 neonates were appropriate for GA (AGA), and 29 were small GA (SGA). The baseline nutrition and postnatal weight changes are provided in Table 1.

The mean GV of AGA neonates was less compared to SGA neonates by 3.13 g/kg/d at 30 days of postnatal life, with a GV of 15.04±4.32 g/kg/d for AGA and 18.17±5.02 g/kg/d for SGA neonates. This difference was statistically significant (p=0.01).




However, there was no significant difference in GV between SGA (19.7±6.1) and AGA (20.27±5.75) infants at 40 weeks of PMA.

Weight of seven neonates was above 10th centile at 40 weeks of PMA, and 21 babies had HC above 10th centile at 40 weeks of PMA. 45% infants were SGA at birth, and at 40 weeks PMA, 76% remained below 3rd centile for weight (of the intra-uterine curves). However, 76% infants had HC >3rd centile (Tables 2 and 3). There was no correlation between energy intake on the day 7 and weight and HC at 40 weeks of PMA.

Clinical sepsis was present in 24.6% of cases while culture positive sepsis was seen in 18.8% cases. Out of the 13 babies with culture-proven sepsis, seven had growth of *Klebsiella*, three had *Staphylococcus aureus*, one had *Enterococcus,* and two had *Enterobacter*. Sepsis was most common among the neonates with 29-32 weeks of gestation which also had a central line inserted for TPN. Other complications include PDA (18.8%), ROP (24.5%), IVH (2.9%), and PVL (1.5%). 9 (13.04%) neonates expired before discharge, out of which 8 neonates expired in the late neonatal period, and 1 expired after the neonatal period.

The overall incidence of dyselectrolytemia was 71% with hyponatremia being the most common abnormality (40.6% cases), followed by hypernatremia in 7.2% and hyperkalemia in 1.4% neonates. 13 neonates had sodium levels between 125 and 129 mEq/L, 9 had levels between 120 and 124 mEq/L, and 6 had sodium <120 mEq/L. Two had apnea due to hyponatremia, and none suffered from seizures. Out of 13 neonates, who had metabolic acidosis, five had clinical sepsis, five had culture-proven sepsis, and three had necrotizing enterocolitis. Urea was elevated in 18.8% neonates receiving TPN; however, only one neonate (1.4%) developed acute kidney injury.

**Table 1: Nutrition and postnatal weight changes**

| Variables | Mean±SD | Median | Range |
|---|---|---|---|
| Age at which enteral feeds started (in days) | 2.5±1.5 | 3 | 1-11 |
| Time to reach full enteral feeds (in days) | 11.3±4.5 | 10 | 5-26 |
| Calorie intake on D7 | 92.6±13.1 | 94 | 62-134 |
| Cumulative wt loss proportion (%) | 8.5±4.7 | 9.0 | 0-21 |
| Number of days to regain birth weight (in days) | 11.1±4.5 | 11 | 0-26 |

**Table 2: Correlation between energy intake on day 7 and weight at 40 weeks PMA**

| Weight centile | Calorie intake on day 7 | | | | p value |
|---|---|---|---|---|---|
| | <100 Kcals/kg/d | | >100 Kcals/kg/d | | |
| | n=38 | % | n=20 | % | |
| <3rd | 31 | 81.6 | 13 | 65 | 0.15 |
| 3rd-10th | 4 | 10.5 | 3 | 15 | |
| 10th-50th | 3 | 7.9 | 4 | 20 | |

**Table 3: Correlation between energy intake on day 7 and head growth at 40 weeks PMA**

| HC centile | Calorie intake on day 7 | | | | p value |
|---|---|---|---|---|---|
| | <100 Kcals/kg/d | | >100 Kcals/kg/d | | |
| | n=38 | % | n=20 | % | |
| <3rd | 11 | 28.9 | 3 | 15 | 0.72 |
| 3rd-10th | 14 | 36.8 | 9 | 45 | |
| 10th-50th | 12 | 31.6 | 7 | 35 | |
| 50th-90th | 1 | 2.6 | 1 | 5 | |

**HC: Head circumference**

Samples for LFT could not be collected at the right time for all infants. Results of liver enzymes were available for 55 neonates, total protein and albumin for 53 neonates, and cholesterol and TGs for 52 neonates. 15.4% neonates had elevated TGs while 17.3% had hypercholesterolemia and elevated liver enzymes in none of the neonates. Hypoalbuminemia with normal total protein content was seen in 4 (7.5%) neonates, out of which three also had culture-proven sepsis. 28.9% neonates developed thrombocytopenia after starting TPN or had decreasing platelet count from that at birth. Among that, 18.8% had sepsis as a confounding factor.

## DISCUSSION

The postnatal weight loss (%), age at which birth weight regained and subsequent weight gain in the present study were similar to the reports by Paul et al., [5] (1991-1997), Wright et al., [6] (1987-1991), and Ehrenkranz et al. [7] (1994-1995). The studies conducted on preterm receiving TPN after the year 1990 show better growth pattern probably due to the improved

nutritional practices in the last two decades. In the present study, mean GV of AGA infants was less compared to that of SGA infants by 3.13 g/kg/day at 30 days of postnatal life. Similar findings were reported earlier by Paul et al. [5] where mean GV of AGA infants was less compared to SGA infants by 3.6 g/kg/day at 30 days of life.

Embleton et al. [8] showed poor weight gain in the postnatal period related to increasing cumulative energy and protein deficits with maximum deficits occurring during the first week of postnatal life. In this study, we compared energy intake on the day 7 (<100/kcal/kg/day and >100 Kcal/kg/day) with weight and HC at 40 weeks PMA which was statistically not significant.

Among the study neonates, we observed clinical sepsis more often than culture positive sepsis. Culture positive sepsis included mostly Gram-negative sepsis. Beganovic et al. [9] reported clinical sepsis in 38.0% and culture positive sepsis in 10.8% among preterm infants receiving TPN. The most common cause for sepsis was *Staphylococcus epidermidis* followed by *S. aureus*. In the study by Beganovic et al., GA was included in logistic regression analysis, but the odds ratio was still high for TPN and sepsis [9].

We provided TPN to <1250 g birth weight neonates in whom the prevalence of PDA is usually high. The incidence of PDA in this population varies between 18 and 77% [10-12]. We did not find any relationship between TPN and PDA in our study. In contrast, in a study by Lee et al. [13] delayed closure of PDA was correlated positively with increased ventilation support, hospitalization, time to full enteral feeds, and duration of TPN.

Poor postnatal weight gain is a predictor of severe ROP. One study reported that infusion of lipids >2 g/kg/day during first 7 days of life was associated with decreased rates of ROP [14]. The authors concluded that the risk of developing severe ROP in extremely premature infants might be reduced by improving nutritional support, specifically targeting lipids and total calories, and thereby improving weight gain. There was no relationship of ROP, IVH, and PVL to TPN administration in the present study.

The incidences of hyponatremia, hypernatremia, and hyperkalemia in our study were lower compared to reported incidences of corresponding electrolyte abnormalities of 61.4%, 23.4%, and 30.3%, respectively, in a study by Jacob et al. [15]. Jacob et al. studied electrolyte abnormalities by multiple measurements and adjusted the fluid and electrolyte infusion once or twice daily. They also reported raised BUN and creatinine in 16.6% of neonates receiving TPN with the mean onset age of 15.6±12.6 days. Only one neonate developed acute kidney injury in the present study. Elevated TG level was observed in lesser percentages of neonates receiving TPN in the present study compared to 62% in a trial carried out by Martin et al. [16]

Our study had few limitations such as small sample size and not enrolling the controls.

## CONCLUSION

Conventional TPN mimics intra-uterine growth until 30 days of postnatal life. However, catch-up growth at 40 weeks of PMA was not satisfactory which indicate that growth at 40 weeks of PMA depends on other factors besides TPN. Mean GV of AGA infants was found to be lower compared to that in SGA infants at 30 days of postnatal life. Besides hyponatremia, there was no major complication due to TPN in this study.

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