Effect of Parenteral Nutrition-Associated Factors on the Growth of Premature Infants

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Abstract: *Objective*: To investigate the factors that affect the growth of preterm infants who receive parenteral nutrition (PN).

Methods: A retrospective cohort study was performed in Uttaradit hospital, Thailand, using data collected between January 2012 and July 2016. The main outcome measure was postnatal growth failure (PGF), comprising weight gain rate at 36 weeks, weight at 36 weeks, time to regain birth weight and growth failure at 36 weeks.

Results: Eighty preterm infants were included in this study, with a mean gestational age of 32 weeks and birth weight of 1468 grams. Multiple regression analysis indicated that the time to achieve full enteral feeding (r = 0.33, 95% CI[0.01,0.48]) was associated with the weight gain rate at 36 weeks of corrected age, birth weight (r = -0.53, 95% CI[-445.04, -216.70]) was associated with weight at 36 weeks of corrected age, the initial timing of PN (r = -0.24, 95% CI[-4.10, -0.40]), average amount of protein in PN (r = 0.39, 95% CI[0.55, 3.43]) and the initial amount of protein in PN (r = -0.46, 95% CI[-3.19, -1.00]) were associated with the time to regain birth weight, and a birth weight classified as small for gestational age (SGA, OR = 15.90, 95% CI[1.54,164.14]) was significantly associated with growth failure at 36 weeks of corrected age.

Conclusions: The results of this study indicate that both nutrition and non-nutrition factors affect PGF in preterm infants who receive PN.

Keywords: Premature, preterm, growth failure, factors, postnatal growth failure.

INTRODUCTION

Postnatal growth failure (PGF) is commonly observed in preterm infants, and these infants are often well below the 10th percentile of postmenstrual age at discharge [1-3]. The National Institute for Child and Human Development (NICHD) Neonatal Research Network reported that 97% of very low birth weight infants (VLBW) had growth failure at 36 weeks corrected age [3]. Improved nutritional support for extremely low birth weight infants (ELBW) has been associated with better growth and improved neurodevelopmental outcomes [4-6]. Increased first-week protein and energy intakes of ELBW infants are associated with improved neurodevelopment outcomes at 18 months [7]. Infants who received aggressive PN resulted in rapid increase in weight, length and head circumferernce [8]. Aside from the nutritional factors, non-nutrition factors such as birth weight and comorbidities (severe respiratory distress syndrome, patent ductus arteriosus, sepsis, necrotising enterocolitis and bronchopulmonary dysplasia) have been found to be associated with PGF [9,10].

This retrospective cohort study investigated both nutrition and non-nutrition factors affecting the growth of preterm infants who received parenteral nutrition (PN).

MATERIALS & METHODS

This study was approved by ethical review committee, the Faculty of Pharmacy, Chiang Mai University. Because of the retrospective design, informed consent was waived. This retrospective cohort study included preterm infants born at Uttaradit Hospital in Thailand between January 2012 and July 2016. The inclusion criteria were preterm infants with a birth weight <2500 g who received PN and who continued treatment at Uttaradit hospital. Exclusion criteria were the presence of major congenital anomalies, bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA, treated with medication or operation), necrotising enterocolitis (NEC, classified as stage 3 according to the classification of Bell *et al*. [11]), intraventricular haemorrhage (IVH, classified as grade 3 according to the grading system of Papile *et al*.

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ISSN: 2223-3806 / E-ISSN: 1927-5951/20

[12]) and proven sepsis. The original study population consisted of 262 infants. Of these infants, 182 were excluded from the study due to comorbidities (n = 95), missing data (n = 39), death (n = 34) or transfer to another hospital (n = 14). The remaining 80 infants were deemed eligible for inclusion in the study.

Definitions and Data Collection

The definition of preterm infants was a gestational age of <37 weeks. Gestational age was performed by physicians using the new Ballard score [13]. The PN administered to infants was composed of at least dextrose and amino acids. The corrected age was calculated using the chronologic age and adjusted for gestational age. Birth weight was classified according to birth weight for gestations appropriate for gestational age (AGA; birth weight between the 10^{th} and 90^{th} percentile) or small for gestational age (SGA; birth weight below 10^{th} percentile) [14].

Data were collected by reviewing the medical charts. Demographic data included the birth weight, gestational age, 5-minute Apgar scores and gender. Nutritional data included daily weight, PN fluid volume and its composition (amino acid, dextrose and lipid), enteral nutrition (EN; breast milk) volume, timing of initiation of PN and its composition, timing of initiation of EN, duration of PN, time to full EN and time to regain birth weight.

Calculation

The outcomes were analysed from the first day of PN until the end of PN or 36 completed weeks corrected age.

For PN, the average energy intake (Kcal/kg/day) was calculated as the sum of amino acid (4 kcal/g), dextrose (3.4 kcal/g) and lipid (9 kcal/g) intake. The average amount of each nutrient (amino acid, dextrose, lipid; g/kg/day) was calculated as the grams of each nutrient per kilogram per day.

For EN (breast milk), the calculation method was similar to PN based on Mimouni's study [15].

Outcomes

The outcome of PGF and was assessed based on four measures:

(1) rate of weight gain at 36 weeks (g/kg/day), calculated according to the formula

Weight gain rate = $(W_2 - W_1) / (t \times W_1)$

W_2 is the weight at 36 weeks of corrected aged (g), W_1 is the birth weight (g) and t is the duration from the first day to regain birth weight until 36 weeks of corrected age.

(2) weight at 36 weeks of corrected age (g)

(3) time to regain birth weight (days), defined as the time period from birth to regain birth weight

(4) growth failure at 36 weeks, defined as bodyweight <10^{th} percentile of the standard intrauterine growth curve of Thai neonates delivered at Rajavithi Hospital [14] at 36 weeks of gestational age.

Statistical Analysis and Variables

Continuous variables were summarised as the mean ± standard error for parametric data and the median (interquartile range) for non-parametric data. Categorical data were expressed as the number (percentage). Univariate analysis was conducted to identify factors associated with the weight gain rate at 36 weeks, weight at 36 weeks of corrected age and time to regain birth weight. Pearson's correlation coefficient and Spearman's rank test were used for the parametric and non-parametric continuous variables, respectively. Binary logistic regression was used to identify factors associated with growth failure at 36 weeks of corrected age. Variables with a p-value less than 0.20 in the univariate analyses were entered into the multivariate analysis. For the multivariate analysis, we applied multiple linear regression to identify factors associated with the weight gain rate at 36 weeks, weight at 36 weeks of corrected age and time to regain birth weight, and also used multiple logistic regression to analyse growth failure at 36 weeks of corrected age. Statistical significance was set at a p-value less than 0.05. All of the analyses were performed using SPSS version 18.

The sample size was calculated using the formula devised by Hair and *et al*. [16] (number of variables × 10). Eight variables were to be analysed, including average energy intake (PN and EN), average nutrient intake (PN and EN), time of starting PN, initial nutrient intake (PN), time to full EN, birth weight (SGA and AGA), gestational age and 5-minute Apgar scores. Therefore, based on the formula, at least 80 subjects were required to represent the population.

RESULTS

Eighty preterm infants were included in the final analyses. The majority of them were male, with mean gestational age of 32.01±1.25 weeks and mean birth weight of 1468.75±260.51 grams. Overall, 73.75% of the subjects were SGA and 26.25% were AGA. Detailed demographic data are summarised in Table **1**. Information on nutritional intake and growth outcomes are presented in Table **2**.

Table 1: Demographics and Characteristics of Preterm Infants

Demographics/characteristics	
Males[a]	45 (56.25)
5-minute APGAR score[b]	7.79±3.03
Gestational age (weeks)[b]	32.01±1.25
Birthweight (g)[b]	1468.75±260.51
SGA[a]	59 (73.75)

SGA = small for gestational age.
[a]number of cases (percentage); [b] Mean ±SD.

Correlations between variables and PGF (weight gain rate at 36 weeks of corrected age, weight at 36 weeks of corrected age and time to regain birthweight) are presented in Table **3** as the results of multiple linear regression analysis.

The time until complete EN was significantly associated with the weight gain rate at 36 weeks of corrected age. Therefore, infants who required a longer time to reach full EN would have a greater weight gain rate at 36 weeks of corrected age.

Birthweight was significantly associated with the weight gain rate at 36 weeks of corrected age. Preterm infants with SGA have a lower average weight at 36 weeks corrected age than those who are AGA.

Table 2: Parenteral Nutrition (PN) and Enteral Nutrition (EN) Intakes and Growth Outcomes

Nutrition Intakes of preterm infanats	
Time PN was started (h)[a]	
Min–max (h)	26.00 (14.25,60.50)
Time PN was started[b]	2–152
<48 h	58 (72.50)
≥48 h	22 (27.50)
Duration of PN (days)[a]	11.00 (8.00,16.75)
Full EN time (days)[c]	17.40 ±8.00
Energy intake (kcal/kg/day)[c]	
PN	72.91 ±15.34
EN	28.47 ±11.41
PN and EN	101.38 ±15.13
Amino acid intake (kcal/kg/day)[c]	
PN	3.88 ±0.82
EN	0.81 ±0.33
PN and EN	4.69 ±0.76
Dextrose intake (kcal/kg/day)[c]	
PN	10.67 ±2.87
EN	2.73 ±1.09
PN and EN	13.63 ±2.60
Lipid intake (kcal/kg/day)[c]	
PN	2.26 ±0.92
EN	1.38 ±0.60
PN and EN	3.61 ±0.90
Initial nutritional intake from PN (g/day)	
Amino acid[c]	2.31 ±0.93
Dextrose[c]	7.08 ±1.20
Lipid[a]	1.00 (1.00,2.00)
Growth Outcomes of preterm infants	
Weight gain rate at 36 weeks of corrected age (g/kg/day)[c]	16.50 ±5.87
Weight at 36 weeks of corrected age (g)[c]	1876.38±276.43
Time to regain birth weight (days)[c]	10.68 ±4.21
Growth failure at 36 weeks of corrected age[b]	72 (90)

[a]Median (IQR); [b]number of cases (percentage); [c]Mean±SD.

Table 3: Correlations between Variables and Postnatal Growth Failure According to Multiple Linear Regression Analysis

Variable	Beta [95% CI]	p-value
Weight gain rate at 36 weeks of corrected age		
Time to achieve full EN (days)	0.33[0.01, 0.48]	0.043
Weight at 36 weeks of corrected age		
Birth weight	-0.53[-445.04, -216.70]	<0.001
Time to regain birth weight		
Time PN was started (h)	-0.24 [-4.10, -0.40]	0.018
Amino acids from PN (g/kg/day)	0.39 [0.55, 3.43]	0.007
Amino acid intake on the first day of PN (g/day)	-0.46 [-3.19, -1.00]	<0.001

Table 4: Correlations between Variables and Postnatal Growth Failure According to Multiple Linear Regression Analysis

Variable	Adjusted OR [95% CI]	p-value
Growth failure at 36 weeks of corrected age		
Amino acid intake on the first day of PN (g/day)	0.48 [0.14, 1.73]	0.192
5-minute Apgar scores	1.10 [0.85, 1.40]	0.482
Gestational age	1.65 [0.86, 3.17]	0.134
Birth weight	15.90 [1.54, 164.14]	0.020
- SGA	1	
-AGA		

SGA = small for gestational age; AGA = appropriate for gestational age.

The time to start PN, average amount of amino acids from PN and amino acid intake on the first day of PN were associated with the time to regain birth weight. Preterm infants who received PN within 48 hours after birth took less time to regain their birth weight compared to those infants who received PN after 48 hours of birth. As for the average amount of amino acids received from PN, this study found that infants who received a high average amount of amino acids took longer to regain birth weight. Conversely, preterm infants with low amino acid intake on the first day of PN showed an increased time to regain birth weight.

Correlations between variables and PGF (growth failure at 36 weeks of corrected age) are presented in Table 4 as the results of multiple logistic regression analysis. Birth weight was significantly associated with growth failure at 36 weeks of corrected age. Preterm SGA infants were found to be 15 times more likely to have PGF at 36 weeks of corrected age than AGA infants when controlling for four variables (amino acid intake on the first day of PN, 5-minute Apgar score, gestational age and birth weight).

DISCUSSION

This study showed that both nutritional and non-nutritional factors affect the growth of preterm infants who receive PN. The time of starting PN was associated with the time to regain birth weight. Preterm infants who received PN within 48 hours of birth took a shorter time to regain birth weight compared to those infants who received PN after 48 hours. This finding is in accordance with a study by Moyses *et al.*, [17] which revealed that infants who received early PN (within 48 hours after birth) took less time to regain birth weight than those who received late PN (more than 48 hours after birth). Moreover, early PN improved weight at discharge or at 36 weeks postmenstrual age, and it did not affect morbidity and mortality. This is because preterm infants are likely to encounter growth failure due to various factors. Among them are nutrition-related factors, which have a significant effect. Therefore, receiving PN soon after birth could enhance the growth of preterm infants and is associated with a positive nitrogen balance and caloric intake [18,19].

The time until full EN was significantly associated with the weight gain rate at 36 weeks of corrected age. Infants who took longer to reach full EN had a higher weight gain rate at 36 weeks of corrected age. The goal when feeding VLBW infants is to achieve full enteral feeding in the shortest time while maintaining optimal growth and nutrition, and avoiding the adverse consequences of rapid advancement of feeding. Furthermore, EN is preferred to PN because PN is associated with a host of complications including vascular catheterisation, sepsis and other adverse effects [20-22]. The results of the current study are in contrast to previous studies, which found that those infants who took a shorter time to reach full EN gained weight faster; [23] however, this difference could be explained by different outcome measurements between studies.

This study found that infants with higher protein intake, measured as the average amount of amino acids received from PN, took a longer time to regain their birth weight. Preterm infants require more protein to maintain sufficient energy and a positive nitrogen balance, and protein is also essential for ensuring normal foetal growth and development [22,24]. The majority of previous studies report that increasing the amount of protein administered to preterm infants benefits their growth [25,26] However, the results of our study show the opposite effect. This was probably because our research aimed to investigate the average amount of protein given to only one group of preterm infants through PN, but most previous studies compared two groups that were given different average amounts of protein. In the current study, preterm infants with a low amino acid intake on the first day of PN took longer to regain their birth weight. Those preterm infants who received a higher average amount of protein from PN took more time to regain birth weight. According to a study by Porceli *et al*., [26] the group of infants given an increased amount of amino acids from the beginning gained more weight. This finding is consistent with this research, which found that starting with a high amount of amino acids from PN could reduce the time to regain birth weight in preterm infants. However, a study by Burattini *et al*. [27] reported that increasing the amount of amino acids from PN did not affect weight gain at 36 weeks of age.

Carbohydrates are a very important source of energy. In PN, carbohydrates are essential nutrients for infants, required to prevent hypoglycaemia and to provide energy for protein anabolism and growth [28]. Hyperglycaemia is a major adverse effect of excessive carbohydrate administration during PN, caused by a decreased insulin concentration and increased gluconeogenesis [29]. This research also revealed that the average amount of carbohydrate from PN, enteral feeding, and the timing of initiation of carbohydrate from PN and EN are not correlated with the growth of preterm infants. With that said, no previous studies have suggested a correlation between the amount of carbohydrates and growth. Most of them likely mentioned the effect of increasing energy with total protein, carbohydrate and lipid in PN, and results were examined with respect to growth because increasing amounts of carbohydrates can have significant side effects. One of these is hyperglycaemia, which requires close monitoring of blood sugar levels.

Lipids in PN represent a source of energy, prevent essential fatty acid deficiency and deliver lipid-soluble vitamins [30]. Most previous studies compared the starting time to receiving lipids from PN. One study reported that the cumulative intake of parental lipids during the first week is positively associated with weight gain up to 28 days of life [31]. However, this research did not find a correlation between the average amount of lipids from PN, full enteral feeding and the starting amount of lipids from PN with the growth of preterm infants. This is probably because lipids administration requires monitoring of the triglyceride level to prevent hypertriglyceridemia, and lipids administration should be stopped or reduced in case of infection in infants, which could result in discontinued or reduced fat intake in some infants. This might not have affected the growth of preterm infants in this study.

Regarding gestational age, this research did not find an association between gestational age and postnatal growth. These results are in contrast to a previous study that showed negative associations between gestational age and growth at 0 to 56 and 0 to 14 days [32]. The study by Merry *et al*. measured growth over the period of 0 to 56 days of age and found a mean change in weight. However, the current study examined infants at the corrected age of 36 weeks, which could explain the differences in research outcomes. A study by Fenton *et al*. concluded that a variety of methods could be used to summarise the growth rate of preterm infants due to the lack of standardisation of methods [33].

Infant birth weight is correlated with average weight at the corrected age of 36 weeks. Those infants who are SGA will have a lower average weight at the corrected age of 36 weeks than those who are AGA. This research also found that the birth weight is correlated with growth failure at 36 weeks. That is, SGA infants presented more than 15 times higher likelihood of growth failure at 36 weeks than AGA infants. This result is consistent with a previous study, which showed an association of weight z-score <-2 with corrected age at discharge for SGA infants. In addition, the likelihood of growth restriction at discharge was 2.6 times higher in SGA infants [34].

In conclusion, this study assessed the factors that affect the growth of preterm infants who receive PN and found that both nutrition-related factors (initiation time of PN, time to reach full EN, the average amount of protein and the initial amount of protein from PN) and non-nutrition-related factors (birth weight, SGA), had a significant effect on the growth failure of preterm infants ($p<0.05$). Using the factors examined in this research, it is possible to develop PN protocols for preterm infants in clinical practice. Furthermore, we developed the starter PN solution to be instantly used that was suitable for neonates born out of hours. In addition, this standard PN formulations in preterm infants were standardized to ensure proper nutrients.

SOURCE OF FUNDING

Funding was not received for this study.

CONFLICT OF INTEREST

None of the authors has a conflict of interest with regard to the manuscript.

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Received on 19-04-2020 Accepted on 20-06-2020 Published on 31-07-2020

DOI: https://doi.org/10.29169/1927-5951.2020.10.04.2