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Use of Concentrated Parenteral Nutrition Solutions Is Associated With Improved Nutrient Intakes and Postnatal Growth in Very Low-Birth-Weight Infants

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Abstract

Background: Evidence showing the beneficial effects of enhanced parenteral nutrition (PN) to very low-birth-weight (VLBW, <1500 g) infants is accumulating. However, PN composition and its impact on growth outcomes are questioned. This study aimed to investigate the associations between administration of a concentrated PN regime and intakes of energy and macronutrients as well as postnatal growth in VLBW infants. **Methods:** We compared 2 cohorts of VLBW infants born before ($n = 74$) and after ($n = 44$) a concentrated PN regime was introduced into clinical use. Daily nutrition and fluid intake during the first 28 postnatal days and all available growth measurements during hospitalization were retrospectively collected from clinical charts. **Results:** Infants who received concentrated PN compared with original PN had higher parenteral intakes of energy (56 vs 45 kcal/kg/d, $P < 0.001$), protein (2.6 vs 2.2 g/kg/d, $P = 0.008$), and fat (1.5 vs 0.7 g/kg/d, $P < 0.001$) during the first postnatal week. Changes in standard deviation scores for weight and length from birth to postnatal day 28 were more positive in the concentrated PN group (mean [95% CI]; weight change: $-0.77 [-1.02 \text{ to } -0.52]$ vs $-1.29 [-1.33 \text{ to } -1.05]$, $P = 0.005$; length change: $-1.01 [-1.36 \text{ to } -0.65]$ vs $-1.60 [-1.95 \text{ to } -1.25]$, $P = 0.025$). There were no significant differences in fluid intake and infant morbidity between the groups. **Conclusion:** Our results suggest that concentrated PN is useful and seems to be safe for improving early nutrition and growth in VLBW infants. (*JPEN J Parenter Enteral Nutr.* 2020;44:327–336)

Keywords

amino acids; energy intake; nutrient intakes; parenteral nutrition; postnatal growth; very low-birth-weight infants

Clinical Relevancy Statement

This before-and-after study explored the effects of a concentrated parenteral nutrition regime as compared with a previously used original parenteral nutrition regime in infants with a birth weight <1500 g. Infants who received the concentrated regime had higher nutrition intake during

the first 2 postnatal weeks. Weight and length gain were improved during postnatal weeks 2–4 and at a postmenstrual age of 36 weeks. This concentrated parenteral nutrition regime is an efficient way of providing early nutrition to very low-birth-weight infants without being associated with enhanced fluid intakes or increased infant morbidity.

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Introduction

Preterm-born infants, in particular those infants born with a very low birth weight (VLBW, <1500 g), are at high risk for malnutrition and postnatal growth failure.^{1,2} This increased risk of malnutrition is a consequence of the extraordinarily high nutrient requirements of VLBW infants in combination with the practical challenges involved in the provision of these nutrients via enteral nutrition and parenteral nutrition (PN) for these infants.^{3,4}

Nutrition is a key factor for normal cell growth, and many nutrients are essential for brain development.⁵ Starvation for just 1 day can be detrimental for VLBW infants. Suboptimal nutrition and growth during early life may have a long-lasting impact on health outcomes, with effects lasting into adulthood.⁶⁻⁹ Providing the right amount, quality, and composition of nutrients during sensitive periods is essential for normal growth and development of organ systems.^{10,11}

To prevent malnutrition and growth failure in VLBW infants during early postnatal life, PN is required and should be introduced as soon as possible after birth.^{9,12} Early administration of PN in VLBW infants induces an anabolic state, which has been shown to be both safe and well tolerated by the infants.^{13,14} A meta-analysis demonstrated that early PN induced improvement in short-term growth outcomes without evidence of increased morbidity or mortality.¹⁵

However, the provision of adequate nutrition in preterm infants during the first postnatal weeks is challenging, and intakes often do not reach the recommended levels.^{1,16,17} A common problem is a clinical need for fluid restriction because of morbidities, such as respiratory distress syndrome and patent ductus arteriosus (PDA), which limits the amount of fluid available for PN and thus may lead to reduced energy and macronutrient intakes.

To meet contemporary recommendations, without increasing fluid intake, a concentrated PN regime was introduced at a neonatal intensive care unit at a tertiary university hospital in Sweden. We hypothesized that infants who received a concentrated PN regime would have higher intakes of energy and protein and would show improved postnatal growth as compared with infants who received the previous original PN regime.

Methods

Study Design and Population

This study was designed as a single-center retrospective observational study comparing 2 cohorts of VLBW infants who received a PN regime either before or after a concentrated PN regime was implemented into clinical use. Both PN regimes were based on standardized PN solutions with the possibility to complement with additive nutritional

products according to an individual assessment by the attending physician.

Two groups of VLBW infants were included in the study: (1) infants born between February 1, 2010, and February 18, 2012, before the concentrated PN regime was implemented (original PN group: $n = 81$); and (2) infants born between February 19, 2012, and September 30, 2013, after the concentrated PN regime was implemented (concentrated PN group: $n = 53$). These infants represented the entire VLBW infant population admitted to the neonatal intensive care unit at Umeå University Hospital, Sweden, within 24 hours after birth and treated there for ≥ 7 days, between February 1, 2010, and September 30, 2013. Data collection ended on September 30, 2013, because of a further alteration of the PN protocol.

Infants with chromosomal or severe congenital anomalies known to affect nutrition intake and/or growth were excluded from the analyses. Therefore, in the original PN group, 1 infant was excluded because of gastrointestinal malformation and a second infant because of skeletal malformation, whereas in the concentrated PN group, 1 infant was excluded because of gastrointestinal malformation, 2 infants because of congenital heart disease, and 2 infants because of Down syndrome. Furthermore, infants with posthemorrhagic hydrocephalus were excluded from the analyses because of expected nonphysiological growth measurements (original PN group: $n = 5$; concentrated PN group: $n = 2$). Two additional infants who received concentrated PN were excluded: 1 because of complete lack of nutrition records and the other because of not receiving the concentrated PN regime during the first 8 postnatal days. In total, 74 infants were included in the original PN group and 44 infants in the concentrated PN group.

PN

Aside from the implementation of the concentrated PN regime, no changes in PN care were introduced during the study period. The 2 PN regimes each consisted of 2 separate bags. Original PN was a pharmacy-prepared all-in-one solution combined with an adjustable glucose bag with electrolytes, whereas concentrated PN was a commercially available glucose/amino acid/electrolyte solution (Numeta G13, Baxter Medical AB, Stockholm, Sweden) combined with a separate lipid bag (based on soybean oil, medium chain triglycerides, olive oil, and fish oil [SMOF], Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany) with vitamins (Table 1). All PN bags were always available at the neonatal intensive care unit, allowing for immediate administration of PN once a central line was placed.

At the discretion of the attending physician, some infants received additional parenteral amino acid, glucose, and/or lipid solutions. The composition of the 2 different PN regimes are therefore based on (1) macronutrients provided

Table 1. Nutrition Content of Original and Concentrated PN Regime Given to Very Low-Birth-Weight Infants.

Nutrients	Original PN	Concentrated PN
Main bag		
Macronutrients		
Glucose, g/100 mL	6.84	16.70
Amino acids, g/100 mL	2.72	3.90
Lipids, g/100 mL	1.66	
Minerals	Yes ^a	Yes ^b
Vitamins	Yes ^a	No
Additional bag	Glucose bag with individual adjusted minerals	Lipid bag (SMOF) with vitamins ^c

PN, parenteral nutrition; SMOF, based on soybean oil, medium chain triglycerides, olive oil, and fish oil.

^aContains sodium, potassium, calcium, phosphate, magnesium, zinc, copper, selenium, manganese, iodine, vitamin A, vitamin D, vitamin E, vitamin K, thiamin, riboflavin, niacin, vitamin B6, folic acid, vitamin B12, biotin pantothenic acid, and vitamin C.

^bContains sodium, potassium, calcium, phosphate, magnesium, chloride, and the individual adjusted minerals zinc, copper, selenium, manganese, and iodine; vitamins are routinely supplied from an additional lipid bag.

^cContains vitamin A, vitamin D, vitamin E, vitamin K, thiamin, riboflavin, niacin, vitamin B6, folic acid, vitamin B12, biotin pantothenic acid, and vitamin C.

by the PN regimes; and (2) additionally provided parenteral amino acids, lipids, and/or glucose (Table 2). Moreover, the majority of infants in both groups received flush solutions containing amino acids, which are not included in Table 2 but are included in all following calculations of total and parenteral nutrient intakes.

Data Collection

All nutrition, growth, and laboratory data were collected retrospectively from clinical charts using a computer-aided nutrition calculation program (Nutrium software by Nutrium AB, Umeå, Sweden). Data collection included (1) daily parenteral and enteral nutrition and fluid intake during the first 28 postnatal days; (2) all available postnatal growth measurements (weight, length, and head circumference [HC]) during hospital stay; and (3) daily measurements of pH, base excess, and glucose concentrations (highest concentration) during the first postnatal week. For infants transferred to lower-level hospitals, data collection was continued using clinical charts from the respective hospitals.

Perinatal and morbidity data were prospectively collected within the Swedish Neonatal Quality register and included gestational age (GA) at birth, sex, multiple pregnancy, prenatal steroid treatment, Apgar score at 5 minutes, duration of mechanical ventilation treatment, duration of antibiotics treatment, treatment of PDA, insulin treatment,

Table 2. Average Composition of the 2 PN Regimes Based on Actual Intakes on Postnatal Day 4.^a

Macronutrient	Original PN	Concentrated PN	P-Value
	(n = 73) ^b	(n = 43) ^b	
	Mean ± SD	Mean ± SD	
Glucose, g/100 mL	10.60 ± 1.65	12.04 ± 2.61	<0.001
Amino acids, g/100 mL	2.27 ± 0.54	3.02 ± 0.78	<0.001
Lipids, g/100 mL	1.18 ± 0.79	2.73 ± 1.09	<0.001

Amino acids from flush solutions are not included in the calculations. Independent samples *t*-test.

PN, parenteral nutrition; SD, standard deviation.

^aInfants received the highest amount of PN at postnatal day 4.

^bOne infant in each group did not receive PN at postnatal day 4.

postnatal steroid treatment, necrotizing enterocolitis, intra-ventricular hemorrhage, bronchopulmonary dysplasia, and sepsis. Data regarding retinopathy of prematurity (ROP) were collected from the Swedish ROP register (SWEDROP).

Data Management

Glucose, amino acids, and lipids are henceforth referred to as carbohydrates, protein, and fat, respectively. Nutrition intakes were analyzed as total, parenteral, and enteral intakes of energy (kcal/kg/d), carbohydrates (g/kg/d), protein (g/kg/d), and fat (g/kg/d). Nutrient intakes were calculated using manufacturer-supplied nutrient content data for each nutritional product. Breast milk samples were routinely analyzed for energy and macronutrient contents using midinfrared spectrophotometry analyses (MilkoScan 4000, FOSS, Hillerød, Denmark) at Eurofins Steins Laboratory AB in Jönköping, Sweden. In case breast milk was not analyzed, macronutrient contents were assumed to be equal to the average content of the analyzed breast milk samples expressed ≤ 28 postpartum days. Total nutrition and PN intakes included transfused blood products, in which the contents were calculated from published values.^{18,19} All nutrition intakes on the day of birth (day 0) were corrected for time of birth.

For days with missing anthropometric measurements, the infant weight, length, and HC values were calculated by linear interpolation. To allow for comparisons at different GAs, measurements of postnatal growth parameters were transformed into standard deviation scores (SDS) for GA using a Swedish gender-specific growth reference for infants born after 24 weeks of GA.²⁰ For infants born before 24 weeks of GA, a Canadian reference was used.²¹ In 5 cases for which length and/or HC at birth were not available, measurements on the first or second postnatal day were used as birth measurements. Small for GA (SGA) status was defined as a birth weight > 2 SD below the mean.

In the case of infant death, early discharge, and/or partially unobtainable nutrition, morbidity, or growth data on the day of birth, infants were included in the analyses as far as possible. If mothers started with breastfeeding and weekly total fluid intake decreased by 10% or more, data collection was ceased. Therefore, patient numbers in the original and concentrated PN groups differed between 64–74 and 41–44 infants, respectively, depending on the parameter and time point analyzed.

Enteral Nutrition

For the vast majority of infants, enteral nutrition consisted exclusively of mothers' own breast milk or donor breast milk and was initiated as soon as possible after birth. According to the clinical guideline, breast milk was fortified with human milk fortifier (HMF) when the enteral intake of fluids was about 70–100 mL/kg/d. HMF was individually adjusted according to breast milk macronutrient analysis. Unrelated to our intervention, the manufacturer changed the composition of the HMF in mid-2011. Thus, most of the infants in the original PN group received an HMF that contained 0.40 g protein per sachet, whereas infants in the concentrated PN group received an HMF that contained 0.55 g protein per sachet. The energy content of both HMFs were equal because of a lower carbohydrate content of the latter HMF. Fat content did not differ between the HMFs.

Clinical Definitions

Necrotizing enterocolitis was defined as stage 2 or higher, according to Bell's classification.²² ROP was classified according to the international classification of ROP.²³ Intra-ventricular hemorrhage was graded according to the Papile classification.²⁴ Bronchopulmonary dysplasia was defined as having an oxygen requirement at 36 weeks postmenstrual age (PMA). Treatment of PDA included both pharmacological and surgical intervention. Metabolic acidosis was defined as having a pH <7.30 in combination with a base excess of <−5 mmol/L, occurring at least once during the first postnatal week. Hyperglycemia was defined as a glucose concentration >10 mmol/L, occurring at least once during the first postnatal week.

Statistical Analyses

The prespecified primary outcome was a change in SDS for weight from birth to postnatal day 28. An a priori power analysis showed that, allowing for a dropout rate of 15%, the group size required to detect a difference of 0.3 SD in weight SDS with a power of 80% was 60 participants, using a 2-tailed test and a significance level of 5%. Statistical analyses were performed with IBM SPSS Statistics (Version 24.0 and 25.0 for Windows; IBM Corp., Armonk, NY, USA). For comparisons between the 2 PN groups,

independent samples *t*-test (for continuous variables) and Fisher's exact probability test (for categorical variables) were used. Two-way between-group analysis of variance was used to test for interactions between confounding factors. Continuous variables are expressed as mean ± SD, whereas categorical variables are expressed as number (percentage), unless otherwise noted. *P*-values < 0.05 were considered significant.

Ethics

The regional ethical committee at Umeå University, Sweden (Dnr 2011-417-31 M, 2012-458-31 M, and 2017-35-32 M), approved the study.

Results

Baseline Characteristics

There were no significant differences in baseline characteristics between the 2 groups concerning GA, Apgar score at 5 minutes, sex, SGA status, prenatal steroid treatment, birth weight, birth length, and birth HC (Table 3). Weight and HC at birth, adjusted for GA using SDS, did not differ significantly between the groups, whereas birth length SDS was significantly lower among infants who received concentrated PN compared with infants who received original PN. More twin pregnancies were observed in the concentrated PN group compared with the original PN group. The concentrations of all macronutrients in the 2 PN regimes differed significantly (Table 2).

Nutrition Intakes

PN was the main source of energy during postnatal days 0–5 and supplied on average 27% of the energy intake during the second postnatal week (postnatal days 7–13; Figure 1; Table 4).

Infants in the concentrated PN group received significantly higher parenteral and total energy intakes during postnatal days 1–5 and 1–10, respectively, compared with infants in the original PN group (Figure 1). During the first and second postnatal weeks, infants in the concentrated PN group had 21% and 7% higher daily total energy intakes, respectively (*P* < 0.001 and *P* = 0.007; Figure 1; Table 4). Enteral energy intakes did not differ between the 2 groups during the first 4 postnatal weeks.

Daily total intakes of protein during the first (postnatal days 0–6), second, and third postnatal week (postnatal days 14–20) were 19%, 15%, and 9% higher, respectively, in the concentrated PN group compared with the original PN group (Table 4; postnatal week 3: 4.0 ± 0.7 vs 3.6 ± 0.5 g/kg/d, *P* = 0.004). During the first postnatal week, daily parenteral protein intake was significantly higher in the concentrated PN group. Daily total and parenteral intakes

Table 3. Baseline Characteristics and Clinical Conditions During Hospitalization in Very Low-Birth-Weight Infants Who Received Either an Original or a Concentrated PN Regime.

Characteristics	Original PN (n = 69–74) ^a Mean ± SD	Concentrated PN (n = 41–44) ^a Mean ± SD	P-Value
Baseline characteristics			
Gestational age, weeks	26.9 ± 2.7	27.4 ± 2.3	0.369 ^b
Birth weight, g	919.0 ± 318	920.0 ± 303	0.986 ^b
Birth weight, SDS	−1.3 ± 1.4	−1.7 ± 1.64	0.128 ^b
Birth length, cm	34.9 ± 4.2	34.1 ± 3.7	0.353 ^b
Birth length, SDS	−1.4 ± 1.7	−2.3 ± 1.78	0.007 ^b
Birth head circumference, cm	24.3 ± 2.8	25.0 ± 2.3	0.180 ^b
Birth head circumference, SDS	−0.8 ± 0.9	−0.7 ± 0.84	0.435 ^b
Apgar at 5 minutes	7.4 ± 1.5	7.1 ± 1.7	0.329 ^b
	n (%)	n (%)	
Sex, male	39 (52.7)	26 (59.1)	0.568 ^c
Small for gestational age	20 (27.0)	14 (31.8)	0.675 ^c
Prenatal steroid treatment	66 (94.3)	42 (97.7)	0.648 ^c
Multiple pregnancy	11 (14.9)	17 (38.6)	0.006 ^c
Clinical conditions during hospitalization			
	Mean ± SD	Mean ± SD	
Duration of mechanical ventilation treatment, days	12.2 ± 15.9	11.0 ± 14.7	0.676 ^b
Duration of antibiotics treatment, days	21.8 ± 19.7	18.4 ± 16.4	0.346 ^b
	n (%)	n (%)	
Insulin treatment	21 (28.4)	7 (15.9)	0.179 ^c
Postnatal steroid treatment (oral or injection)	24 (32.4)	15 (34.1)	1.000 ^c
Treated patent ductus arteriosus	34 (45.9)	12 (27.3)	0.052 ^c
Necrotizing enterocolitis	5 (6.8)	1 (2.3)	0.409 ^c
Severe intraventricular hemorrhage (grades 3 or 4)	2 (2.7)	4 (9.1)	0.196 ^c
Bronchopulmonary dysplasia	22 (30.1)	14 (31.8)	0.840 ^c
Sepsis	24 (32.4)	12 (27.3)	0.680 ^c
Severe retinopathy of prematurity (stages 3–5)	15 (21.7)	8 (19.5)	1.000 ^c
Metabolic acidosis during postnatal week 1	44 (60.3)	24 (54.5)	0.567 ^c
Hyperglycemia during postnatal week 1	39 (53.4)	28 (63.6)	0.336 ^c

PN, parenteral nutrition; SDS, standard deviation score.

^aDifferent patient numbers due to unobtainable morbidity or growth data at the day of birth.

^bIndependent samples *t*-test.

^cFisher's exact probability test.

of fat during the first and the second postnatal weeks were higher in the concentrated PN group compared with the original PN group. Daily intakes of enteral protein and fat did not differ significantly between the groups during any of the first 4 postnatal weeks (data for postnatal weeks 3 and 4 not shown). During the first postnatal week, daily total and enteral intakes of carbohydrates were higher in the concentrated PN group compared with the original PN group.

Neither daily total nor parenteral nor enteral fluid intakes differed significantly between the groups during any of the first 4 postnatal weeks (Table 4; data for postnatal weeks 3 and 4 not shown). The proportions of fluid given parenterally to the original PN group during postnatal weeks 1, 2, 3, and 4 were 70%, 32%, 18%, and 12%, respectively, and did not differ significantly from the concentrated PN group (66%, 28%, 16%, and 10%, respectively).

Postnatal Growth

Weight, length, and HC measurements were available on average (\pm SD) for 21.5 (\pm 6.6), 4.0 (\pm 1.2), and 4.8 (\pm 2.7) days, respectively, during the first 28 postnatal days. Changes in weight and length SDS from birth to postnatal days 7–28 were less negative in the concentrated PN group compared with the original PN group (Figure 2; Table 5). At a PMA of 36 weeks, infants who received concentrated PN compared with original PN still had a less negative change in weight SDS (mean [95% CI]: -0.02 [-0.28 to 0.24] vs -0.57 [-0.86 to -0.28]; $P = 0.006$) and length SDS (Table 5). Infants in the original PN group had improved growth in HC during the first 28 postnatal days as well as at a PMA of 36 weeks compared with infants in the concentrated PN group (not significant). Absolute changes in weight, length, and HC from birth to postnatal day 28 are shown in Supplementary Table S1.

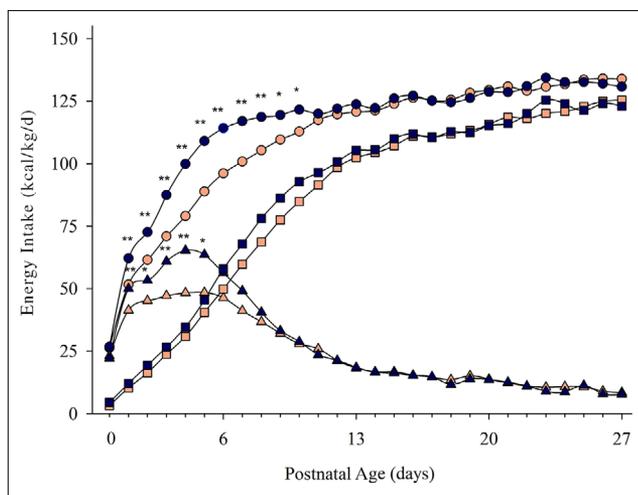


Figure 1. Mean intakes of energy during the first 28 postnatal days in infants who received either original or concentrated parenteral nutrition (PN; original PN group: $n = 68$ to 74 and concentrated PN group: $n = 43$ to 44 at different time points due to infant death, early discharge, or unobtainable nutrition data). —○—, total intake in infants who received original PN; —●—, total intake in infants who received concentrated PN; —△—, parenteral intake in infants who received original PN; —▲—, parenteral intake in infants who received concentrated PN; —□—, enteral intake in infants who received original PN; —■—, enteral intake in infants who received concentrated PN. * P -value < 0.01 ; ** P -value < 0.001 . kcal, kilocalorie; kg, kilogram

Clinical Outcomes

No statistically significant differences were found between the groups regarding duration of mechanical ventilation treatment, duration of antibiotics treatment, insulin treatment, postnatal steroid treatment, treatment of PDA, and the incidence of necrotizing enterocolitis, severe intraventricular hemorrhage (grades 3–4), bronchopulmonary dysplasia, sepsis, severe ROP (stages 3–5), metabolic acidosis, and hyperglycemia (Table 3).

Discussion

The results of this study show that a change to a concentrated PN regime improves nutrition intakes as well as postnatal growth in VLBW infants without being associated with adverse events.

The increased total energy and macronutrient intakes during the first postnatal week were mainly explained by higher parenteral macronutrient intakes, with a 20% higher parenteral protein intake and a 110% higher parenteral fat intake, resulting in a 21% higher total energy intake in the concentrated PN group. The increased parenteral intakes during the first postnatal week coincided with improved weight gain, which began to appear on postnatal days

3–4, became significant on postnatal day 7, and remained significant until postnatal day 28 as well as at a PMA of 36 weeks. No differences in weight change were observed during the first 3 postnatal days, suggesting that weight change during the first 3–4 days of life in VLBW infants was caused only by shifts in fluid balance and was not dependent on nutrient intakes. This is in line with the lack of observed effects on growth in intervention studies in which additional parenteral proteins and/or fats have been given only during the first 3–4 days of life.^{13,25}

In a before-and-after study by Izquierdo et al, an optimized PN protocol including higher recommended macronutrient intakes led to increased weight gain on postnatal day 14, but this positive effect did not remain significant on postnatal day 28.²⁶ The authors did not observe any differences in length and HC gain between the groups. In contrast to their findings, our results showed significantly increased weight gain beyond postnatal day 14. We also observed significantly increased length gain during postnatal weeks 2–4. A possible explanation for the increased growth pattern in our study, compared with the aforementioned study, might be that in our study the concentrated PN group received increased total protein and fat intakes even during postnatal week 2, whereas Izquierdo et al did not observe any differences in macronutrient intake beyond the first postnatal week. Moreover, in the aforementioned study, infants who received the optimized PN protocol did not reach the recommended nutrient intake, whereas our study showed that most infants who received the concentrated PN regime achieved the recommended nutrient intake.

The results of the present study are in agreement with the results from the before-and-after study of Miller et al, who studied 2 different PN protocols during the transition phase administered to infants born at <32 weeks of gestation, with a birth weight <2000 g.²⁷ The transition phase was defined as the provision of enteral nutrition volumes of 20 mL/kg until full feeds (160 mL/kg). Infants who received the concentrated PN protocol had significantly higher energy and protein intakes during the transition phase. At the end of the transition phase, infants in the study group had significantly higher weight SDS compared with the control group. This difference persisted at a PMA age of 35 weeks. Growth velocity during transition was significantly higher in the study group compared with the control group.

In a randomized controlled trial, Morgan et al compared 2 PN regimes that differed in energy and macronutrient concentrations.²⁸ Infants who received the concentrated PN regime showed increased weight and HC gain compared with the control group. Our results are in agreement with the higher rate of weight gain up to postnatal day 28 and to a PMA of 36 weeks, observed by Morgan et al. However, we did not find any significant association between nutrition intake and HC gain in our study, but rather a nonsignificant

Table 4. Average Daily Total, Parenteral, and Enteral Intakes of Macronutrients and Fluids During Postnatal Weeks 1 and 2 in Very Low-Birth-Weight Infants Who Received Either an Original (n = 71–74)^a or a Concentrated (n = 44) PN Regime.

Postnatal Period PN regime	Energy kcal/kg/d Mean ± SD	Protein g/kg/d Mean ± SD	Fat g/kg/d Mean ± SD	Carbohydrates g/kg/d Mean ± SD	Fluid mL/kg/d Mean ± SD
Postnatal week 1					
Total intake					
Original PN	72 ± 8.0	2.7 ± 0.7	2.1 ± 0.7	10.3 ± 1.1	131 ± 19
Concentrated PN	87 ± 7.0	3.3 ± 0.5	3.0 ± 0.5	11.7 ± 1.0	136 ± 15
<i>P</i> -value	<0.001	<0.001	<0.001	<0.001	0.110
Parenteral intake					
Original PN	45 ± 14	2.2 ± 0.9	0.7 ± 0.5	7.7 ± 2.0	93 ± 32
Concentrated PN	56 ± 16	2.6 ± 0.8	1.5 ± 0.7	8.3 ± 2.1	89 ± 27
<i>P</i> -value	<0.001	0.008	<0.001	0.102	0.534
Enteral intake					
Original PN	26 ± 14	0.6 ± 0.4	1.4 ± 0.8	2.7 ± 1.5	38 ± 20
Concentrated PN	30 ± 18	0.7 ± 0.4	1.5 ± 0.9	3.4 ± 1.9	47 ± 25
<i>P</i> -value	0.169	0.236	0.473	0.045	0.054
Postnatal week 2					
Total intake					
Original PN	113 ± 15	3.4 ± 0.5	4.9 ± 1.2	13.2 ± 1.7	167 ± 14
Concentrated PN	120 ± 13	3.9 ± 0.4	5.4 ± 0.9	13.6 ± 1.3	165 ± 14
<i>P</i> -value	0.007	<0.001	0.017	0.215	0.466
Parenteral intakes					
Original PN	28 ± 23	1.2 ± 1.1	0.6 ± 0.8	4.5 ± 3.5	53 ± 44
Concentrated PN	31 ± 27	1.3 ± 1.1	1.1 ± 1.0	4.1 ± 3.7	45 ± 40
<i>P</i> -value	0.629	0.580	0.014	0.508	0.276
Enteral intakes					
Original PN	84 ± 34	2.2 ± 1.0	4.3 ± 1.7	8.7 ± 3.7	113 ± 43
Concentrated PN	90 ± 36	2.6 ± 1.1	4.3 ± 1.7	9.5 ± 4.0	120 ± 46
<i>P</i> -value	0.443	0.057	0.904	0.263	0.418

Independent samples *t*-test.

PN, parenteral nutrition; SD, standard deviation.

^aDifferent patient numbers due to infant death.

trend in the opposite direction. In a multicenter randomized controlled trial, Uthaya et al noted a smaller HC at term in the infant group that received higher amounts of parenteral protein delivered within 24 hours after birth.²⁹ That study was not powered to detect a difference in this secondary outcome, and the authors identified no between-group differences in brain volume. However, head swelling and molding is often present after preterm birth, and no adjustments to increase the accuracy of HC measurements have been made in our study because of its retrospective nature. Therefore, we cannot exclude measurement errors that could influence our results.

Very brief interventions (duration 3–4 days) including increased protein and/or fat intake have not shown any effects on either growth or neurodevelopmental outcomes.^{13,25} Furthermore, no effect on weight and length gain as well as body composition has been shown when increasing parenteral protein intake beyond the first 3 days without increasing energy intake.^{25,29} In contrast, studies that explored the effects of improved parenteral energy and macronutrient

intakes beyond the first few postnatal days, the present study included, have shown improved postnatal growth patterns in preterm infants with a birth weight <2000 g.²⁶⁻²⁸

In the present study, daily total fluid intake did not differ between the groups during any of the first 4 postnatal weeks. This suggests that a restriction of fluid intake might be an important factor that contributes to inadequate energy and macronutrient intake in VLBW infants who receive a less concentrated PN regime.

More infants in the concentrated PN group were born after a twin pregnancy compared with the original PN group in our study. In the majority of cases, twin birth was associated with a lower birth weight compared with singleton birth.³⁰ However, in our study, birth weight did not differ between the infant groups, and the results did not change when adjusting the models for twin birth.

Infants in the concentrated PN group were less often treated for PDA compared with infants in the original PN group (nonsignificant difference, *P* = 0.052). To the best of our knowledge, no association between nutrition intake

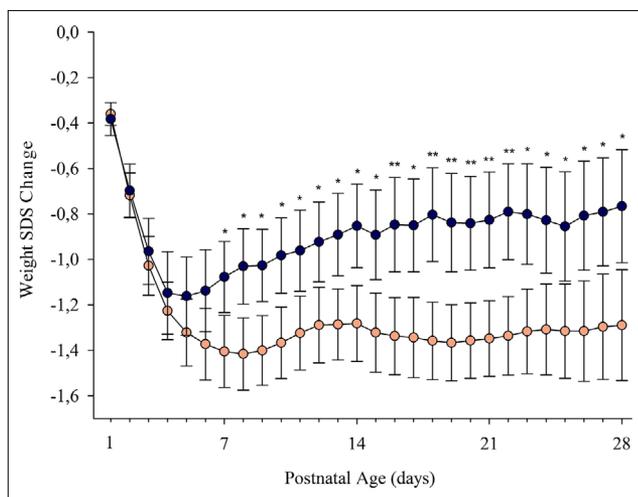


Figure 2. Changes in weight standard deviation scores (SDS) on postnatal days 1 to 28 in infants who received either original (—○—) or concentrated parenteral nutrition (—●—), relative to birth weight as baseline (Original PN group: n = 71 to 74 at different time points due to infant death; Concentrated PN group: n = 44). Values are expressed as 95% confidence intervals for mean of change. **P*-value < 0.01; ***P*-value < 0.001. SDS, standard deviation score.

and the occurrence of PDA has been reported previously. In the clinical setting, fluid restriction is sometimes considered in order to prevent and treat PDA. Since total fluid intake during postnatal weeks 1–4 did not differ significantly between the infant groups in our study, it is not likely that the PDA outcome was influenced by the change of PN regime.

The strengths of this study include the detailed clinical charts, an extensive data acquisition, and a comparison at a uniform age of 36 postmenstrual weeks. Limitations of the study include the before-and-after design including a lack of randomization, a retrospective data collection, and a relatively small sample size, which reduces the power to detect group differences in health outcomes. A further limitation is the individually adapted nutrition practices at the neonatal intensive care unit, including the addition of nutritional products in some cases, the flexible starting point of HMF introduction, and the slight change of the HMF composition. The continuous education of the staff might have led to a more optimal feeding of the infants in the later study period and therefore might influence our results to a minor extent. The flexibility regarding the introduction of the HMF and its change in protein content might explain the improved enteral intakes of carbohydrates and protein (not significant) in the concentrated PN group during the first and second postnatal week, respectively. These improved enteral intakes contributed to the significantly higher total intakes. However, aside from the implementation of the concentrated PN regime, no major changes in either parenteral or enteral nutrition were introduced during the study period.

Our results are of clinical importance because they suggest that a relatively easily implemented change in clinical routines was associated with a significant change in nutrition intakes as well as in weight and length development up to postnatal day 28. The differences in weight and length gain were still significant at a PMA of 36 weeks. Prevention of malnutrition may improve brain development and reduce the risk of ROP in extremely preterm

Table 5. Growth in Length and HC in Very Low-Birth-Weight Infants Who Received Either an Original or a Concentrated PN Regime.

Growth Parameter	Original PN (n = 64–74) ^a Mean [95% CI]	Concentrated PN (n = 41–44) ^a Mean [95% CI]	<i>P</i> -Value
Length SDS change from birth to:			
Postnatal day 7	-0.88 [-1.06 to -0.69]	-0.58 [-0.80 to -0.36]	0.043
Postnatal day 14	-1.32 [-1.57 to -1.08]	-0.79 [-1.08 to -0.50]	0.006
Postnatal day 21	-1.52 [-1.82 to -1.21]	-0.94 [-1.29 to -0.60]	0.017
Postnatal day 28	-1.60 [-1.95 to -1.25]	-1.01 [-1.36 to -0.65]	0.025
PMA of 36 weeks	-1.09 [-1.43 to -0.74]	-0.24 [-0.64 to 0.16]	0.002
HC SDS change from birth to:			
Postnatal day 7	-0.76 [-0.88 to -0.64]	-0.92 [-1.05 to -0.78]	0.091
Postnatal day 14	-1.01 [-1.16 to -0.87]	-1.10 [-1.27 to -0.93]	0.439
Postnatal day 21	-1.02 [-1.19 to -0.85]	-1.25 [-1.47 to -1.03]	0.091
Postnatal day 28	-1.04 [-1.24 to -0.83]	-1.25 [-1.52 to -0.99]	0.196
PMA of 36 weeks	-0.47 [-0.76 to -0.19]	-0.76 [-1.05 to -0.48]	0.182

Independent samples *t*-test.

HC, head circumference; PMA, postmenstrual age; PN, parenteral nutrition; SDS, standard deviation score.

^aDifferent patient numbers due to infant death and/or unobtainable growth data at the day of birth.

infants.^{5,7,8} However, the use of PN is still questioned, and there is a need for high-quality studies to determine the optimal amount, combination, and timing of nutrition intake, which lead to improved short-term and long-term health outcomes.

We conclude that changing to concentrated PN solutions that aim to provide the recommended intake of energy and macronutrients is associated with improved nutrient intake and postnatal growth in VLBW infants, without being associated with adverse events. The use of concentrated neonatal PN solutions might be an effective way of providing early nutrition to VLBW infants.

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Statement of Authorship

M. Domellöf contributed to the conception and design of the research; M. Domellöf contributed to the interpretation of the data; E. S. Sjöström, I. Zamir, and C. Späth contributed to the acquisition, analysis, and interpretation of the data; and C. Späth drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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