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Brief Parenteral Nutrition Accelerates Weight Gain, Head Growth Even in Healthy VLBWs

Naho Morisaki1,2,*, Mandy B. Belfort3,4, Marie C. McCormick5,6, Rintaro Mori1, Hisashi Noma1,7, Satoshi Kusuda8, Masanori Fujimura9, the Neonatal Research Network of Japan

1 Department of Health Policy, National Center for Child Health and Development, Setagayaku, Tokyo, Japan, 2 Department of Pediatrics, University of Tokyo, Bunkyouku, Tokyo, Japan, 3 Division of Newborn Medicine, Boston Children’s Hospital, Boston, Massachusetts, United States of America, 4 Harvard Medical School, Boston, Massachusetts, United States of America, 5 Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America, 6 Society, Health, and Human Development, Harvard School of Public Health, Boston, Massachusetts, United States of America, 7 Department of Data Science, The Institute of Statistical Mathematics, Tachikawa Tokyo, Japan, 8 Department of Neonatology, Maternal and Perinatal Center, Tokyo Women’s Medical University, Shinjukuku, Tokyo, Japan, 9 Department of Neonatology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Osaka, Japan

Abstract

Introduction: Whether parenteral nutrition benefits growth of very low birth weight (VLBW) preterm infants in the setting of rapid enteral feeding advancement is unclear. Our aim was to examine this issue using data from Japan, where enteral feeding typically advances at a rapid rate.

Methods: We studied 4005 hospitalized VLBW, very preterm (23–32 weeks’ gestation) infants who reached full enteral feeding (100 ml/kg/day) by day 14, from 75 institutions in the Neonatal Research Network Japan (2003–2007). Main outcomes were weight gain, head growth, and extra-uterine growth restriction (EUGR, measurement <10th percentile for postmenstrual age) at discharge.

Results: 40% of infants received parenteral nutrition. Adjusting for maternal, infant, and institutional characteristics, infants who received parenteral nutrition had greater weight gain [0.09 standard deviation (SD), 95% CI: 0.02, 0.16] and head growth (0.16 SD, 95% CI: 0.05, 0.28); lower odds of EUGR by head circumference (OR 0.66, 95% CI: 0.49, 0.88). No statistically significant difference was seen in the proportion of infants with EUGR at discharge. SGA infants and infants who took more than a week until full feeding had larger estimates.

Discussion: Even in infants who are able to establish enteral nutrition within 2 weeks, deprivation of parenteral nutrition in the first weeks of life could lead to under nutrition, but infants who reached full feeding within one week benefit least. It is important to predict which infants are likely or not likely to advance on enteral feedings within a week and balance enteral and parenteral nutrition for these infants.

Introduction

Guidelines for nutritional support of very low birth weight (VLBW, <1500 grams) and very preterm (<32 completed weeks’ gestation) infants often emphasize parenteral nutrition as the main source of nutrition for the first weeks of life [1,2]. However, some infants are able to advance enteral nutrition quickly, particularly infants fed breast milk [3–6]. Additionally, providing parenteral nutrition has risks, such as infection, thrombosis, and other complications associated with central venous access [7], and cholestasis [8], and also costs more than feeding enterally. Given the important benefits of early enteral feeding [9], as well as the risks and cost inherent to providing parenteral nutrition, it is important to quantify the benefit of parenteral nutrition in the context of rapid advancement of enteral nutrition. In other words, it is important to clarify the extent to which infants who reach full enteral nutrition at a rapid rate also benefit from parenteral nutrition. This information would inform guidelines about the routine vs. selective parental nutrition use for VLBW preterm infants, particularly those infants expected to achieve full enteral feeding at a rapid rate.

The aim of this study was to quantify the growth benefit of parenteral nutrition in VLBW preterm infants who are able to advance enteral feedings rapidly. Our analysis capitalizes on the Japanese experience in which advancement of enteral feeding in the neonatal intensive care unit (NICU) is typically more rapid than in other countries, possibly due to the high rate of breast milk feeding for preterm infants and the low background necrotizing enterocolitis (NEC) rate [10,11]. Historically the rate of NEC is below 1% in VLBW infants in the Japanese Neonatal Research Network, as compared with 7–10% in the U.S. or other...
We hypothesized that despite routine rapid enteral feeding advancement, parenteral nutrition would nonetheless be beneficial to growth.

Methods

Design, Setting, and Participants
We used data from the Neonatal Research Network of Japan (NRN), a multi-center registry of VLBW infants cared for in 75 participating level III perinatal centers in Japan and funded by a grant from the Ministry of Health, Labor and Welfare in 2004. All registered hospitals provided individual patient data including obstetric, delivery, in-hospital care, and follow-up data at age 1.5 and 3 years to the central committee. The central committee identified potential data errors and requested that individual institutions correct data by going back to medical charts when needed. A description of the NRN cohort including morbidities, mortalities, and outcomes at age 1.5 and 3 years, has been reported previously [14–16].

Figure 1 outlines the population used for this analysis. The NRN cohort included 16001 VLBW infants who were hospitalized in 75 level III NICU’s in Japan from January 2003 to December 2007. Of these, 9152 were born at 24–32 weeks of gestation. We excluded infants with major congenital anomalies (n = 477) and infants admitted to the NICU more than 24 hours after birth (n = 126). In the remaining 8349 infants, 61% of the infants reached 100 ml/kg/day full feeding within 14 days, and 16% achieved this within 7 days. As our interest was mainly in the effect of parenteral nutrition on growth in infants who reached full enteral feeding fairly rapidly, we restricted our analysis to infants who reached full feeding within 14 days (n = 5270), of whom 41% (n = 1784) had received parenteral nutrition during admission. We further excluded infants who died before discharge (n = 39), infants discharged after 48 weeks corrected age (n = 348); infants who developed NEC (n = 13) or underwent surgery (n = 385); and infants missing growth data (n = 108). We also excluded 344 subjects due to missing covariate data. Thus our total sample size for analysis was 4005.

Definition of Diseases and Outcomes
Our main exposure was any use of parenteral nutrition during the hospital stay, which the hospitals provided as yes, or no for each subject. No subject was missing this information.

Our main outcome was extra-uterine weight gain and head growth, which we defined as the change in SD score of each measurement from birth to discharge. These SD scores were calculated using sex, parity, and gestational length (by day) specific growth references for birth weight [17] and head circumference, obtained from vaginal deliveries during 2003–2005 in Japan. We also classified infants as being small for gestational age (SGA) or having extra-uterine growth restriction (EUGR), both proxies for intra-uterine and extra-uterine growth. SGA was defined as birth weight being under the 10th percentile of the reference; EUGR was defined as weight and head circumference at less than the 10th percentile at a given postmenstrual age, as compared with infants born at the same gestational age in the reference.

As growth can be affected by different obstetric and pediatric characteristics as well as the wellbeing of the infant, we considered as covariates the following: maternal age, parity, gestational diabetes (GDM), pregnancy induced hypertension (PIH), use of antenatal steroid, multiplicity, route of delivery, gestational length, sex, SD scores of weight and head circumference at birth, Apgar score at 5 minutes, use of mechanical ventilation, stage of intra-ventricular hemorrhage (IVH), diagnosis of bronchopulmonary dysplasia (BPD), periventricular hemorrhage (PVL), and days taken to reach full enteral feeding.

In all analyses we categorized these variables as follows: maternal age (14–20, 20–34, 35–50 years), parity (0, 1, 2 and above) multiplicity (singleton, twin, triplets or more), route of delivery (cesarean or vaginal), Apgar score at 5 minutes (0–4, 5–10), use of ventilation (no ventilation, ventilation for under 7 days, ventilation over 7 days), IVH (no IVH, grade 1–2 IVH, grade 3–4 IVH), and each completed week of gestation at birth (24 to 32 weeks).

Statistical Analysis
First, we compared maternal and infant characteristics between infants who received parenteral nutrition (n = 1604) and those who did not (n = 2401). Next, as extra-uterine growth is affected by both gestational age and intrauterine growth, we stratified our sample by each week of gestation and intrauterine growth status (SGA or not) and examined each of the following across strata as well as by use of parenteral nutrition or not: change in SD scores
of weight and head circumference at admission and discharge, and length of hospitalization in days.

To account for potential confounding by maternal and infant characteristics, and to account for clustering within institutions, we performed generalized linear mixed models (logistic regression with random intercepts) to estimate the effect of parenteral nutrition on our outcomes of interest (weight gain, head growth, odds of EUGR, and days of admission). For selection of confounders we used parity, GDM, PIH, use of antenatal steroid, multiplicity, gestational length, sex, Apgar score at 5 minutes, IVH stage, use of mechanical ventilation, day of reaching full enteral feeding, as well as birth measurements, due to their clinical relevance and usage in previous papers [5,18,19].

We performed all analyses using SAS version 9.3 (SAS Institute, Cary, NC).

Ethics Statement
All information about the infants was collected anonymously, and the stored data were unlinked from individual data. Written informed consent was obtained from the parents or guardians on behalf of each child enrolled in this study before receiving any data. The protocol of this study was approved by the Central Table 1. Maternal and infant characteristics of 4,005 very low birth weight infants of 24–32 weeks’ of gestation who reached full enteral feeding within 2 weeks.

| Maternal Characteristics | Infants who did not receive parenteral nutrition (n = 2401) | Infants who received parenteral nutrition (n = 1604) |
|--------------------------|----------------------------------------------------------|-----------------------------------------------------|
| Maternal age**           | 30.6 (5.1)                                                | 31.2 (5.1)                                           |
| Number of previous deliveries | 0.7 (0.8)                                             | 0.6 (0.8)                                            |
| Number of fetuses        | 1.3 (0.6)                                                | 1.3 (0.6)                                            |
| Gestational diabetes(%)  | 1.6%                                                     | 1.8%                                                |
| Pregnancy induced hypertension(%)  | 19.3%                                                | 19.5%                                               |
| Use of antenatal steroids(%)** | 42.2%                                               | 48.8%                                               |
| Cesarean section (%)     | 77.3%                                                    | 78.0%                                               |
| Infant Characteristics   |                                                         |                                                     |
| Gestational length (weeks)** | 29.7 (2.0)                                         | 28.7 (2.2)                                          |
| Length of stay (days)**  | 75.6 (25.2)                                             | 84.2 (26.8)                                         |
| Apgar score at 5 minutes** | 8.1 (1.4)                                           | 7.7 (1.7)                                           |
| Days to reach 100 ml per kg per day enteral feeding** | 8.9 (2.7)                                           | 10.3 (2.6)                                          |
| Birth Weight (grams)     | 1176 (234)                                               | 1053 (257)                                          |
| Weight for gestational age, at birth (SD) | −0.90 (1.0)                              | −0.94 (1.2)                                         |
| Birth Head Circumference (cms)** | 26.6 (2.0)                                         | 25.7 (2.2)                                          |
| Head Circumference for gestational age, at birth (SD) | −0.20 (0.8)                              | −0.21 (0.8)                                         |
| Weight at discharge (grams)** | 2649 (452)                                         | 2713 (497)                                          |
| Head Circumference at Discharge (cms) | 34.2 (1.8)                                | 34.3 (1.8)                                          |
| Male (%)                 | 49.8%                                                    | 51.8%                                               |
| Mechanical ventilation** | No use (%)                                               | 24.2%                                               |
|                          | Less than 1 week (%)                                    | 33.4%                                               |
|                          | More than 1 week (%)                                    | 42.4%                                               |
| Intra-Ventricular Hemorrhage** | None (%)                                              | 91.0%                                               |
|                          | Grade 1–2 (%)                                           | 7.1%                                                |
|                          | Grade 3–4 (%)                                           | 1.9%                                                |
| PPHN (%)**               | 1.4%                                                     | 2.9%                                                |
| Sepsis (%)**             | 2.1%                                                     | 3.8%                                                |
| BPD (%)**                | 21.6%                                                    | 33.4%                                               |
| PVL (%)                  | 2.8%                                                     | 3.4%                                                |
| EUGR by weight (%)       | 58%                                                      | 58%                                                 |
| EUGR by head circumference (%) | 12%                                                   | 12%                                                 |

Full enteral feeding: 100 ml per kg per day of milk.
*; p<0.05.
**: p<0.005.
doi:10.1371/journal.pone.0088392.t001
Results

In Figure 2a we show the distribution of days until enteral feeding 100 ml/kg/day (full feeding) within 8549 infants without major congenital anomalies and were admitted within 24 hours after birth, by each week of gestation. The distribution was skewed to the right, with 61% of the infants reaching full feeding within 14 days, and 16% achieving this within 7 days. Time to reach full enteral feeding was greater for infants of lower gestational age, but over 50% of infants born in each gestational week reached full feeding within 14 days. This was as expected from the customs in Japanese NICUs which prefer to initiate and increase enteral feeding as soon as possible.

In Figure 2b, we show the wide inter-institutional variation in usage of parenteral nutrition.

In Table 1 we show maternal and infant characteristics for the 4005 infants who reached full enteral feeding by day 14, grouped by whether they received parenteral nutrition.

Infants who received parenteral nutrition were born earlier and were generally sicker, for example they were more likely to have needed mechanical ventilation, were more likely to have BPD, and took longer to reach full enteral feeding. Those receiving parenteral nutrition also had lower weight and smaller head circumference at birth, but showed higher weight and larger head circumference at discharge.

In Figure 3 we show the average change in weight and head circumference SD from birth to discharge, as well as length of stay, for infants who received and did not receive parenteral nutrition, stratified by intrauterine growth (SGA and non-SGA) as well as week of gestation. Even after stratification, infants receiving parenteral nutrition showed greater growth in most categories.

Table 2 shows the estimated effect of administering parenteral nutrition on growth and length of stay, adjusted for maternal and infant characteristics listed in Table 1. Infants receiving parenteral nutrition showed greater weight gain and head growth: on average 0.09 (95% confidence interval [CI] 0.02, 0.16) SD greater weight gain and 0.16 (95% CI 0.05, 0.28) SD greater head growth. They also tended to have lower odds of being EUGR by weight (OR 0.85, 95% CI 0.66, 1.08) and head circumference (OR 0.66, 95% CI 0.49, 0.88) at discharge, compared to those not receiving parenteral nutrition. Length of stay was 1.29 (95% CI 0.12, 2.45) days shorter for infants who received parenteral nutrition. There was no significant association of parenteral nutrition with adverse outcomes: BPD (OR: 0.85; 95%CI 0.66–1.08); and PVL (OR: 1.19; 95%CI 0.76–1.87).

Effect modification by weeks of gestation (24–27 weeks or 28–32 weeks), intrauterine growth (SGA or non-SGA), and day to reach full feeding (0–7 days or 8–14 days) were not statistically significant, and though estimates differed slightly for each subgroup, as shown in Figure 4, the all effects were in the same direction.

However, point estimates of the effect of parenteral nutrition was largest in SGA infants and infants who took more than one week until full feeding, and smallest in infants who reached full feeding within a week. Point estimates of increase in weight was largest in SGA infants (0.14SD; 95%CI 0.09, 0.37) and infants reaching full feeding after one week (0.08SD; −0.01, 0.31), and smallest in infants who reached full feeding within one week (0.03SD; 0.22, 0.32). Similarly, point estimates of increase in head circumference was largest in SGA infants (0.35SD; 0.03, 0.73) and smallest in non-SGA infants (0.10SD; 0.15, 0.73) and infants reaching full feeding within one week (0.08SD; −0.25, 0.41). Point estimates for effect on length of stay was also largest in SGA infants and infants born at 28 to 32 weeks of gestation, and

Figure 3. Comparison of infants that received and did not receive parental nutrition, stratified by gestational age and intrauterine growth. A) Change in weight (SD) in situ, B) Change in head circumference (SD) in situ, and C) Length of stay (days), of 4,005 very low birth weight infants of 24–32 weeks of gestation that reached full enteral feeding within 2 weeks. Figure legends for Figure 3: Full enteral feeding: 100 ml per kg per day of milk. PN: parenteral nutrition. SGA: small for gestational age, defined as birth weight <10th percentile for postmenstrual age. doi:10.1371/journal.pone.0088392.g003

Internal Review Board at Tokyo Women’s Medical University, where all data were collected and stored. The database was registered as UMIN000006961.
were administered parenteral nutrition for 24–27 days [27]. Even
average 24–27 days to reach 150 ml/kg/day enteral feeding, and
for on average 32 days [28]. In the Maggio study, subjects took on
day enteral feeding, and were administered parenteral nutrition
study, subjects took on average 32–34 days to reach 110 kcal/kg/
EUGR: Extra-uterine growth restriction; defined as weight or head circumference
to advance enteral nutrition rapidly.

Research to inform optimal nutritional care of the preterm
infant is important because inadequate nutrition leads to poor
growth extraterine growth, which in turn has been linked with
poor later neurocognitive outcomes [20–22]. EUGR is highly
prevalent among VLBW and ELBW infants [20,23] and can be
modified by nutritional practices in the NICU [24,25]

Historically, clinicians have been hesitant to advance enteral
feedings at a rapid rate due to concerns about intestinal
immaturity and the associated risk of NEC, a serious and often
life-threatening complication of preterm birth. [26]. Research
focused on providing earlier parenteral nutrition, such as
intravenous amino acids, has shown a beneficial impact on growth
of VLBW infants [27]. For example, Poindexter reported that
clear provision of amino acids was associated with significantly
better growth at 36 weeks postmenstrual age. Similarly, Maggio
reported changes in parenteral nutrition practice improved growth
outcomes at discharge. Our results are consistent with both of
those studies in supporting the benefit of parenteral nutrition on
growth of VLBW infants.

However, in other studies of early parenteral nutrition and
growth, enteral feedings were advanced slowly. In the Poindexter
study, subjects took on average 32–34 days to reach 110 kcal/kg/
day enteral feeding, and were administered parenteral nutrition
for on average 32 days [28]. In the Maggio study, subjects took on
average 24–27 days to reach 150 ml/kg/day enteral feeding, and
were administered parenteral nutrition for 24–27 days [27]. Even
the recent studies shown in a meta-analysis by Moyses [9] on the
effect of parenteral nutrition on growth, show that time to full feeds
took an average of 15 to 33 days [29–33]. In contrast, in our study
population, enteral feedings were advanced much more quickly,
on average over 8–10 days. To our knowledge, no study prior to
ours has evaluated the impact of parenteral nutrition in the setting
of more rapid advance of enteral feedings.

Additionally, through subgroup analysis we found that overall,
SGA infants and infants reaching full feeding after one week
seemed to benefit most from parenteral nutrition in means of
growth and shorter stay. Infants who reached full feeding within
one week seemed to benefit least. Our findings suggest that it is
important to predict which infants are likely or not likely to
advance on enteral feedings within a week.

Our study has several limitations. First, we did not have data on
the timing or duration of parenteral nutrition. Therefore we had to
exclude infants who would be receiving parenteral nutrition due to
their complications: infants that had NEC, surgery, or died during
hospitalization, and thus we could not set these conditions as
outcomes. However, we were most interested in the effects of
parenteral nutrition in otherwise healthy preterm infants. Second,
although a number of maternal and child characteristics were
available, residual confounding may occur by characteristics of
infants who received parenteral nutrition that could promote their
growth, for instance other differences in nutritional practice.
Finally, our study was conducted in Japan where neonatal
 intensive care practices differ from the U.S. and other countries.
However, our setting provides a unique opportunity to examine
the role of parenteral nutrition for infants who advance quickly on
enteral nutrition, and we believe our findings will be relevant for
non-Japanese populations of VLBW infants as well.

In summary, our results support the use of parenteral nutrition
to improve weight gain and head growth, even among relatively
healthy VLBW infants who reach full enteral feeding within 2
weeks. For infants reaching full enteral feedings in 1 week or less,
the benefit was smaller. These findings will be useful for clinicians
weighing the risks and benefits of providing parenteral nutrition to
very low birth weight infants, particularly those who are expected
to advance enteral nutrition rapidly.

Table 2. Adjusted effect of parenteral nutrition use on weight, head circumference, and length of NICU stay.

| Growth parameters in z-scores | Difference (95% CI) | p-value |
|-------------------------------|--------------------|--------|
| Weight gain (SD)              | 0.09 (0.02, 0.16)  | 0.01   |
| Head growth (SD)              | 0.16 (0.05, 0.28)  | 0.004  |
| Length of stay (days)         | −1.29 (0.12, 2.45) | 0.03   |

| Odds ratio (95% CI) | p-value |
|--------------------|--------|
| EUGR by weight (OR) | 0.85 (0.66, 1.08) | 0.18   |
| EUGR by head circumference (OR) | 0.66 (0.49, 0.88) | 0.005  |

Analysis of 4,005 very low birth weight infants of 24–32 weeks’ gestation who reached full enteral feeding within 2 weeks.

Generalized linear mixed models (logistic regression with random intercepts) used to accounting for clustering within institutions. Adjusted for selected maternal (maternal age, number of previous deliveries, number of fetuses, gestational diabetes, pregnancy induced hypertension, use of antenatal steroids, mode of delivery), and infant (gestational length, sex, birth weight, birth head circumference, Apgar score at 5 minutes, days to reach 100 ml per kg per day enteral feeding, length of stay) characteristics.

Full enteral feeding: 100 ml per kg per day of milk.
EUGR: Extra-uterine growth restriction; defined as weight or head circumference <10th percentile for postmenstrual age.
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nearly null in infants who reached full feeding within a week, were
born under 1000 g, or were born at 24–27 weeks of gestation.

Discussion

We observed that among VLBW preterm (24–32 weeks’
gestation) infants who reached full enteral feedings within 2 week
of birth, those infants provided with parenteral nutrition demon-
strated greater weight gain and head growth, and a lower
prevalence of EUGR by weight, as compared with those who did
not receive parenteral nutrition. To the best of our knowledge, this
study is the first to show that parenteral nutrition promotes weight
gain even in preterm infants who are able to advance enteral
nutrition at a fairly fast rate.

Research to inform optimal nutritional care of the preterm
infant is important because inadequate nutrition leads to poor
growth extraterine growth, which in turn has been linked with
poor later neurocognitive outcomes [20–22]. EUGR is highly
prevalent among VLBW and ELBW infants [20,23] and can be
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Figure 4. Estimated effect of administering parenteral nutrition. A) Change in weight (SD in situ), B) Change in head circumference (SD in situ), and C) Length of stay (days). Analysis of 4,005 very low birth weight infants of 24–32 weeks of gestation who reached full enteral feeding within 2 weeks. Legends for Figure 4: Generalized linear mixed models (logistic regression with random intercepts) used to accounting for clustering within institutions. Adjusted for selected maternal (maternal age, number of previous deliveries, number of fetuses, gestational diabetes, pregnancy induced hypertension, use of antenatal steroids, mode of delivery), and infant (gestational length, sex, birth weight, birth head circumference, Apgar score at 5 minutes, days to reach 100 ml per kg per day enteral feeding, length of stay) characteristics. Full enteral feeding: 100 ml per kg per day of milk.

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The Neonatal Research Network of Japan consists of the following institutions (Director, Neonatal Research Network of Japan): Fujimura M (Director, Neonatal Research Network of Japan); Kusuda S (Associate Director, Neonatal Research Network of Japan); Hattori S (Sapporo City General Hospital); Noro A (Kushiro Red Cross Hospital); Amizuka T (Aomori Prefectural Central Hospital); Chida S (Iwate Medical University); Takahashi R (Sendai Red Cross Hospital); Arai H (Akita Red Cross Hospital); Imamura T (Fukushima Medical University); Ujiie N (NationalFukushima Hospital); Miyazono Y (University of Tsukuba); Shimizu T (Nagoya City Women’s Medical Center); Otani H (Dokkyo Medical University); Kono Y (Jichi Medical University); Shimizu M (Saitama Children’s Medical Center); Kunikata T (Saitama Medical University Saitama Medical Center); Fujii T (Gunma Children’s Medical Center); Sato H (Kameda Medical Center); Kondo T (Tokyo Women’s Medical University Yachiyo Medical Center); Watanabe T (Tokyo Metropolitan Bokuto Hospital); Aiwa M (Nagoya University); Ichihara A (Tokyo Women’s Medical University); Makimoto M (Nihon University Itabashi Hospital); Hoshijima J (Tokyo University); Yoda H (Toho University); Kawakami Y (Japan Red Cross Medical Center); Ishii N (Aiiku Hospital); Ito Y (National Center for Child Health and Development); Itani H (Kanagawa Children’s Medical Center); Seki K (Yokohama City University Medical Center); Nomura M (Tokai University); Nowatari M (Kitazato University); Nemoto A (Yamanashi Prefectural Central Hospital); Nagata O (Nagoya Red Cross Hospital); Nagaokawa Y (Nagota City Hospital); Nakamura T (Nagano Children’s Hospital); Okada M (Chitose University); Nakata S (Oita City Hospital); Shimazaki E (National Nagano Hospital); Yoda T (Saku General Hospital); Hutatani T (Toyama Prefectural Central Hospital); Ueno Y (Ishikawa Prefectural Central Hospital); Iwai K (Fukuoka Prefectural Hospital); Nakazawa Y (Shizuoka Children’s Hospital); Oki S (Seiichi Hamamatsu General Hospital); Suzuki C (Nagoya Red Cross First Hospital); Bonomo M (National Mic Hospital); Kawaiwa Y (Gifu Prefectural General Hospital); Nakamura K (Oita Red Cross Hospital); Mitsufuji N (Kyoto Red Cross First Hospital); Shiraiishi J (Osaka Medical Center and Research Institute for Maternal and Child Health); Ichiba H (Osaka City General Hospital); Minami H (Takatsuki City Hospital); Wada H (Yodogawa Christian Hospital); Ohashi A (Kansai Medical University); Sumi K (Azabuhashi Hospital); Takahashi Y (Nara Medical University); Okutani T (Wakayama Prefectural Medical University); Yoshimoto S (Hyogo Prefectural Kobe Children’s Hospital); Nagata I (Tottori University); Kato E (Shimane Prefectural Central Hospital); Watabe S (Kurashiki Central Hospital); Kagynama M (National Okayama Hospital); Fukuhara R (Hiroshima Prefectural Hospital); Hayashitani M (Hiroshima City Hospital); Hasegawa K (Yamaguchi Prefectural Medical Center); Ohita A (National Kagawa Children’s Hospital); Kuboi T (Kagawa University); Akiyoshi S (Elme Prefectural Central Hospital); Kikkawa K (Kochi Health Sciences Center); Satjio T (Tokushima University); Shimokawa S (St. Mary’s Hospital); Matsumoto N (Kitakyushu City Municipal Medical Center); Kanda H (Kurume University); Oota E (Fukuoka University); Kanda G (National Kyushu Medical Center); Ochiai M (Kyushu University); Aoki M (National Nagasaki Medical Center); Kondo Y (Kumamoto City Hospital); Iwai M (Kumamoto University); Iida K (Oita Prefectural Hospital); Ikemoto T (Miyazaki University); Ibarna S (Kagoshima City Hospital); Kokama M (Okinawa Chubu Hospital).

Author Contributions

Conceived and designed the experiments: NM. Performed the experiments: NM. SK MF. Analyzed the data: NM MBB MCM RM. Wrote the paper: NM MBB. Interpreted the data: NM MBB MCM RM. Reviewed and contributed to drafting the final manuscript: RM HN SK MF.

References

1. Ehrenkranz RA (2007) Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol 31: 48–55.
2. Denna SC, Poindexter BB (2007) Evidence supporting early nutritional support with parenteral amino acid infusion. Semin Perinatol 31: 56–60.

3. Kennedy KA, Tyson JE, Charnavanakij S (2008) Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants. Cochrane Database Syst Rev: Cd001241.

4. Bombell S, McGuire W (2009) Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev: Cd000504.

5. Ehrenkrantz RA (2010) Early nutritional support and outcomes in ELBW infants. Early Hum Dev 86 Suppl 1: 21–25.

6. Uihing MR, Das UG (2009) Optimizing growth in the preterm infant. Clin Perinatol 36: 165–176.

7. Blanco CL, Falck A, Green BK, Cornell JE, Gong AK (2008) Metabolic responses to early and high protein supplementation in a randomized trial evaluating the prevention of hyperkalemia in extremely low birth weight infants. J Pediatr 153: 535–540.

8. Hughes CA, Talbot IC, Ducker DA, Harran MJ (1983) Total parenteral nutrition in infancy: effect on the liver and suggested pathogenesis. Gut 24: 241–248.

9. Moyes HE, Johnson MJ, Leaf AA, Cornelius VR (2013) Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J Clin Nutr 97: 816–826.

10. Isayama T, Lee SK, Mori R, Kasuda S, Fujimura M, et al. (2012) Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. Pediatrics 130: e557–965.

11. Kasuda S, Fujimura M, Uchihaya A, Tosu S, Matsunami K (2012) Trends in mortality and mortality among very-low-birth-weight infants from 2003 to 2008 in Japan. Pediatr Res 72: 531–538.

12. Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, et al. (2002) Growth in the preterm infant: can we catch up? Semin Perinatol 27: 302–310.

13. Yee WH, Soraisham AS, Shah VS, Aziz K, Yoon W, et al. (2012) Incidence and mortality of very-low-birthweight infants at 3 years of age born in 2003–2004 in Japan. Pediatrics 130: e957–965.

14. Kono Y, Mishina J, Yonemoto N, Kusuda S, Fujimura M (2011) Outcomes of parenteral nutrition in extremely low birth weight infants. Pediatrics 128: e899–906.

15. Martin CR, Brown YF, Ehrenkranz RA, O'Shea TM, Allred EN, et al. (2009) Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 124: 649–657.

16. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wraze LA, et al. (2006) Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 117: 1253–1261.

17. Ehrenkranz RA, Das A, Wraze LA, Poindexter BB, Higgins RD, et al. (2011) Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res 69: 522–529.

18. Belfort MB, Gillman MW (2013) Healthy infant growth: what are the trade-offs in the developed world? Nestle Nutr Inst Workshop Ser 71: 171–184.

19. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA (2003) Growth failure in the preterm infant: can we catch up? Semin Perinatol 27: 302–310.

20. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, et al. (2009) First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics 123: 1337–1343.

21. Dinerstein A, Nieto RM, Solana CL, Perez GP, Otheguy LE, et al. (2006) Early and aggressive nutritional strategy [parenteral and enteral] decreases postnatal growth failure in very low birth weight infants. J Perinatol 26: 436–442.

22. Higgins RD, Devaskar S, Hay WW Jr, Ehrenkranz RA, Greer FR, et al. (2012) Executive summary of the workshop “Nutritional Challenges in the High Risk Infant”. J Pediatr 160: 511–516.

23. Maggio I, Cota F, Gallini F, Lauriola V, Zecca G, et al. (2007) Effects of high versus standard early protein intake on growth of extremely low birth weight infants. J Pediatr Gastroenterol Nutr 44: 124–129.

24. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, et al. (2009) Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J Clin Nutr 97: 816–826.

25. Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA (2006) Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. J Pediatr 148: 300–305.

26. Aroor AR, Krishnan L, Reyes Z, Fazallulah M, Ahmed M, et al. (2012) Early versus Late Parenteral Nutrition in Very Low Birthweight Neonates: A retrospective study from Oman. Sultan Qaboos Univ Med J 12: 33–40.

27. Garcia LV, Erroz IO, Freire MM, Manuazzi AP, Souto AB, et al. (2012) Does early parenteral protein intake improve extrauterine growth in low birth weight preterms? An Pediatr (Barc) 76: 127–132.

28. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, et al. (2009) First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics 123: 1337–1343.

29. Belfort MB, Rivas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, et al. (2011) Infant growth before and after term: effects on neurodevelopment in preterm infants. Pediatrics 128: e899–906.

30. Dinerstein A, Nieto RM, Solana CL, Perez GP, Otheguy LE, et al. (2006) Early and aggressive nutritional strategy [parenteral and enteral] decreases postnatal growth failure in very low birth weight infants. J Perinatol 26: 436–442.

31. Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA (2006) Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. J Pediatr 148: 300–305.

32. Aroor AR, Krishnan L, Reyes Z, Fazallulah M, Ahmed M, et al. (2012) Early versus Late Parenteral Nutrition in Very Low Birthweight Neonates: A retrospective study from Oman. Sultan Qaboos Univ Med J 12: 33–40.

33. Garcia LV, Erroz IO, Freire MM, Manuazzi AP, Souto AB, et al. (2012) Does early parenteral protein intake improve extrauterine growth in low birth weight preterms? An Pediatr (Barc) 76: 127–132.

34. Janeiro P, Cunha M, Marques A, Moura M, Barroso R, et al. (2010) Caloric intake and weight gain in a neonatal intensive care unit. Eur J Pediatr 169: 99–105.

35. Garcia LV, Erroz IO, Freire MM, Manuazzi AP, Souto AB, et al. (2012) Does early parenteral protein intake improve extrauterine growth in low birth weight preterms? An Pediatr (Barc) 76: 127–132.

36. Janeiro P, Cunha M, Marques A, Moura M, Barroso R, et al. (2010) Caloric intake and weight gain in a neonatal intensive care unit. Eur J Pediatr 169: 99–105.

37. Trintis J, Donohue P, Aucott S (2010) Outcomes of early parenteral nutrition for premature infants. J Perinatol 30: 493–497.

38. Blanco CL, Gong AK, Schoolfield J, Green BK, Daniels W, et al. (2012) Impact of early and high amino acid supplementation on ELBW infants at 2 years. J Pediatr Gastroenterol Nutr 54: 601–607.