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Analysis of Nutrition Support in Very Low-Birth-Weight Infants With Extrauterine Growth Restriction

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Abstract

Objective: To assess the incidence of extrauterine growth restriction (EUGR) in very low-birth-weight infants (VLBWIs) and evaluate the nutrition factors in VLBWIs associated with inadequate nutrient intakes during hospitalization. *Methods:* A total of 128 VLBWIs were divided into an EUGR group (n = 87) and a non-EUGR group (n = 41). Growth and parenteral nutrition (PN) and enteral nutrition (EN) practices were analyzed. Actual energy and protein intakes were subtracted from recommended energy (120 kcal/kg/d) and protein (3.75 g/kg/d) intakes, and nutrition deficits were calculated. *Results:* Growth restriction was 21.9% at birth and 68.0% at discharge. Compared with established guidelines, PN was started late, and the maximum amino acid intake was low in both groups. EN interruption rate was higher in the EUGR group. The average energy intake in the first day after PN termination was lower in the EUGR group. There were significant differences in actual energy and protein intakes in the 2 groups for several weeks during hospitalization. The cumulative energy and protein deficits were significantly higher in the first 8 weeks and during the third to seventh weeks in the EUGR group, respectively. Step regression analysis showed that there was a significant negative correlation between the cumulative deficit of energy and changes of weight *z*-scores ($r = -0.001$, $P < .05$): as the energy deficit loss increased by 100 kcal, the weight *z*-scores dropped by 0.1 SD. *Conclusion:* Inadequate nutrition intake aggravated the occurrence of EUGR in VLBWIs, especially the energy intake. (*Nutr Clin Pract.* 2019;34:436–443)

Keywords

enteral nutrition; extrauterine growth restriction; growth; infant; nutrition support; parenteral nutrition; very low birth weight infant

Background

Optimal nutrition is critical in the management of small premature infants and in reducing long-term morbidities including extrauterine growth restriction (EUGR; growth values <10th percentile of intrauterine growth expected in accordance with estimated gestational age at discharge[1]) and poor neurodevelopmental outcomes in very low-birth-weight infants (VLBWIs; birth weight [BW] <1500 g).[2-5] In 1977, the American Academy of Pediatrics reported that optimal feeding regimens for low-BW infants should promote postnatal growth at a rate similar to that of intrauterine growth, without imposing stress on the developing metabolic or excretory systems.[6] However, this goal of growth rate is difficult to achieve. More than 50% of VLBWIs were <10th weight-for-age percentile at hospital discharge based on data obtained from the California perinatal health cooperation organization in 2005–2012[7] and the United States.[8] In China, the incidence rate of EUGR is >70%.[9,10]

There are several contributing factors to EUGR,[9] one of which is inadequate nutrient intake during the first weeks of life.[11] Few studies have evaluated the problems related to parenteral nutrition (PN) and enteral nutrition (EN) support, such as premature PN termination and EN disruptions. The objectives of this study were to: (1) retrospectively document growth and nutrition support data to assess EUGR rates and nutrient intakes of VLBWIs, and (2) evaluate the nutrition problems in VLDWIs associated with inadequate nutrient intakes during hospitalization.

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Patients and Methods

Study Design, Participants, and Setting

This retrospective, single-center cohort study was conducted from October 1, 2012, to October 1, 2016, at a neonatal intensive care unit (NICU) of Xinhua Hospital. Preterm infants with BW between 1000 and 1499 g admitted to the NICU were considered eligible. The exclusion criteria were hospital stay <14 days, major congenital anomalies, genetic disorders, and ever fed with human milk (small samples and incomplete data of human milk fortifier). The study was evaluated by the Ethics Committee of Xinhua Hospital. Informed consent was obtained from each caretaker.

Nutrition Policies of the NICU

PN, which was initiated within 24 hours of birth, contained dextrose at an infusion rate of 4–8 mg/kg/min; amino acids (Pediatric Compound Amino Acid injection 18AA-II, PAA 6%; Treeful, Shanghai, China) started at 1.5–2 g/kg/d, increased by 0.5–1.g/kg/d to a maximum of 3.5–4.0 g/kg/d; and lipids (Lipofundin MCT/LCT, 20%; Braun Medical, Melsungen, Germany) started at 1 g/kg/d, increased by 0.5–1 g/kg/d to a maximum of 3 g/kg/d. Energy supplementation was increased based on metabolic tolerance, with a limitation of infusion rates of 11–14 mg/kg/min dextrose, 3.5–4.0 g/kg/d amino acids, and 3 g/kg/d lipids.

In general, EN initiation is recommended within 12 hours of birth. In this study, EN was started depending on the respiratory and circulatory status of each infant. Infants who were clinically stable received minimal enteral feeding (formula) as early as possible after birth started at 10–20 mL/kg/d based on BW and increased by 20–30 mL/kg/d. At EN energy of 100 kcal/kg/d, PN was discontinued. Then EN volumes continued to increase by 20–30 mL/kg/d to reach a volume of 150–165 mL/kg/d or an energy intake of 110–135 kcal/kg/d. During enteral feeding, 5% glucose, hydrolyzed formula, and preterm infant formula were usually administered based on the feeding tolerance of VLBWIs. According to the manufacturers' information, the hydrolyzed milk formula (100 mL) and premature formula (100 mL) had an estimated energy level of 68 and 83 kcal, a protein content of 1.9 and 2.3 g, and a lipid content of 3.4 and 4.2 g, respectively.

Nutrition therapy was prescribed by the attending physician of the Neonatal Department and the clinical nutrition physician of the Pediatric Digestive and Nutrition Department. The attending pediatrician prescribed the implementation of EN based on the condition of each infant and after consultations with the duty physician and nurses. The clinical nutrition physician adjusted PN support according to the amount of enteral feeding and the remaining fluid requirements. PN and EN support were performed according to Chinese Society for Parenteral and Enteral Nutrition guidelines for neonates[12] and preterm infants,[2,3,5] which was drafted by referring to the nutrition guidelines of the United States and Europe.[2,3,5]

Data Collection and Management

Clinical, growth, and nutrition support data were obtained from the electronic medical charts of each infant. The clinical data included information on gestational age, sex, BW, the use of ventilator support, and so on. Small for gestational age (SGA) is defined as BW <10th percentile based on the Fenton 2013 growth chart.[13]

Weight was recorded 3 times a week, specifically on Mondays, Wednesdays, and Fridays, using an electronic digital scale (accuracy ±1 g). Each weighing was performed with no clothes, before the 9 AM feeding, and after a bath. The maximum percentages of weight loss, time to regain BW, and weight gain rates during hospitalization were calculated. The rate of weight gain (g/kg per day) was calculated by the exponential mathematical model described by Patel et al.[14,15] The formula was:

$$\text{Growth velocity} = [1000 \times \ln(W_n/W_1)] / (D_n - D_1)$$

where W_n = discharge weight (g), W_1 = BW (g), D_n = hospital stay of NICU (day), and D_1 = days to regain BW.

Weight was converted to weight *z*-scores (mean, SD) using clinical actual age percentile and *z*-score calculator based on the Fenton 2013 growth chart[13] written with assistance of Dr. Timothy P. Stevens (University of Rochester, Rochester, NY, USA). Changes in weight *z*-scores were calculated from the *z*-score at birth to discharge or the 10th week (almost all of the infants' hospital stays were <10 weeks).

Daily nutrition support during hospitalization was recorded. Nutrient intakes were calculated from the actual intakes obtained from PN and EN, including nutrients present in long-term and temporary intravenous fluids. For PN, we included information on the day of initiation and termination, duration, and initial and maximum intakes of energy, proteins, and lipids. For EN, we collected information on the type of enteral feeding, day of initiation, days to achieve exclusive EN, interruption rates, and energy intake on the first day of EN.

Actual daily nutrient intake of PN and EN was calculated based on recommendations (90 kcal/kg/d for PN and 122.5 kcal/kg/d for EN energy; 3.75 g/kg/d protein for PN and EN).[2,5,12] Total percentage of nutrient intakes was analyzed; nutrient intake was not considered to be sufficient when the sum of the percentages was <100%. Actual nutrient intakes were subtracted from the recommended intakes to calculate daily deficit (120 kcal/kg/d for energy[11] and 3.75 g/kg/d for protein[2,5,12]), which was used to calculate cumulative deficit.

Table 1. Clinical and Growth Characteristics of Newborns During the Hospitalization Period.

Characteristics	Total (n = 128)	EUGR Group (n = 87)	Non-EUGR Group (n = 41)	*P*-Value
Gestational age, weeks	30.8 ± 2.1	31.5 ± 2.1	29.1 ± 1.3	<.001
Male sex, n (%)	62 (48.4)	38 (43.7)	24 (58.5)	.117
Birth weight, g	1310.0 ± 123.8	1296.4 ± 127.7	1310.9 ± 116.0	.537
Small-for-Gestational-Age Infants, n (%)	28 (21.9)	28 (32.2)	0	<.001
Multiple births, n (%)	34 (26.6)	24 (27.6)	10 (24.3)	.722
In vitro fertilization, n (%)	16 (12.5)	8 (9.2)	8 (19.5)	.100
Invasive ventilator, h	51.0 (24.9–114.6)	65.5 (39.3−116.1)	40.4 (12.1−111.1)	.054
Maximum weight loss, g	67.7 ± 54.5	67.8 ± 58.0	67.6 ± 47.2	.989
Days to regain birth weight, d	10.5 ± 5.8	10.3 ± 6.0	10.7 ± 5.3	.717
Growth rate, g/kg/d	14.1 ± 3.2	13.5 ± 3.2	15.6 ± 2.7	<.001

EUGR, extrauterine growth restriction.

Table 2. Characteristics of PN and EN Support.

Characteristics	Total (n = 128)	EUGR Group (n = 87)	Non-EUGR Group (n = 41)	*P*-Value
Time to start PN, h	24 (18–28)	24 (21–29)	20 (10.5−26)	.001
Duration of PN, d	28.8 ± 11.8	30.0 ± 12.9	26.3 ± 8.8	.060
Initial lipid, g/kg/d	1.02 (0.92–1.33)	1.03 (0.94–1.35)	1 (0.83–1.26)	.329
Maximum lipid, g/kg/d	2.14 ± 0.34	2.13 ± 0.35	2.17 ± 0.31	.554
Initial protein, g/kg/d	1.51 ± 0.3	1.53 ± 0.3	1.47 ± 0.34	.326
Maximum protein, g/kg/d	3.1 ± 0.5	3.15 ± 0.48	2.98 ± 0.42	.064
Time to start EN, h	30.6 (21.6–67.3)	37 (22–68.5)	29.8 (46.7–145.0)	.209
Time to start milk, h	79.0 (50–163.4)	92.2 (50–181.3)	78 (46.7–145.1)	.450
Days to reach full feeds	29.8 ± 12.1	31.3 ± 13.2	27.1 ± 9.0	.039
Interrupt rate of EN, n (%)	27 (21.1)	23 (26.4)	4 (9.8)	.031
Energy intake in the first day of total EN, kcal/kg/d	101.6 ± 23.0	97.7 ± 25.3	109.9 ± 14.1	.005
Average of energy intake, g/kg/d	103.2 ± 10.5	100.8 ± 9.3	108.4 ± 11.1	<.001
Average of protein intake, g/kg/d	3.2 ± 0.2	3.15 ± 0.2	3.29 ± 0.3	.003
Average of lipid intake, g/kg/d	4.4 ± 0.7	4.2 ± 0.7	4.7 ± 0.6	.001

EN, enteral nutrition; EUGR, extrauterine growth restriction; PN, parenteral nutrition.

Statistical Analysis

Infants were stratified into a EUGR group and a non-EUGR group. The data were either presented as median and interquartile range (IQR) and compared using the Mann-Whitney *U* test, or as mean ± standard deviation (SD) and compared using the Student *t*-test. The categorical variables were expressed as numbers and percentages and compared using the χ^2 or Fisher exact test. Statistical significance was set at $P < .05$. Multiple linear regression analysis was performed to determine independent variables significantly explaining the variance in changes of weight *z*-scores. Data were analyzed using the SPSS version 19.0 (IBM SPSS Statistics; IBM Corporation).

Results

During the study period, 173 preterm infants with BW <1499 g were admitted to the NICU. Out of these infants, 45 were excluded because of diverse reasons: 8 died at <7 days of age, 20 were transferred out of the NICU, 1 was admitted to the NICU at 1 day of age and was receiving nutrition support out of the NICU, 9 had BW <1000 g, and 7 were breastfed.

The remaining 128 VLBWIs were divided into 2 groups: a EUGR group (n = 87) and a non-EUGR group (n = 41). The clinical and growth characteristics are presented in Table 1. Gestational age was significantly higher in the EUGR group than in the non-EUGR group ($P < .001$), which might be explained by the distribution of SGA infants: all of the SGA infants were in the EUGR group. Growth rate was also significantly lower ($P < .001$) in the EUGR group than in the non-EUGR group.

The characteristics of PN and EN are shown in Table 2. The initiation of PN occurred at a later time point in the EUGR group than in the non-EUGR group ($P = .001$). The number of days to reach full feeds was significantly higher in the EUGR group ($P = .039$). The interruption rate

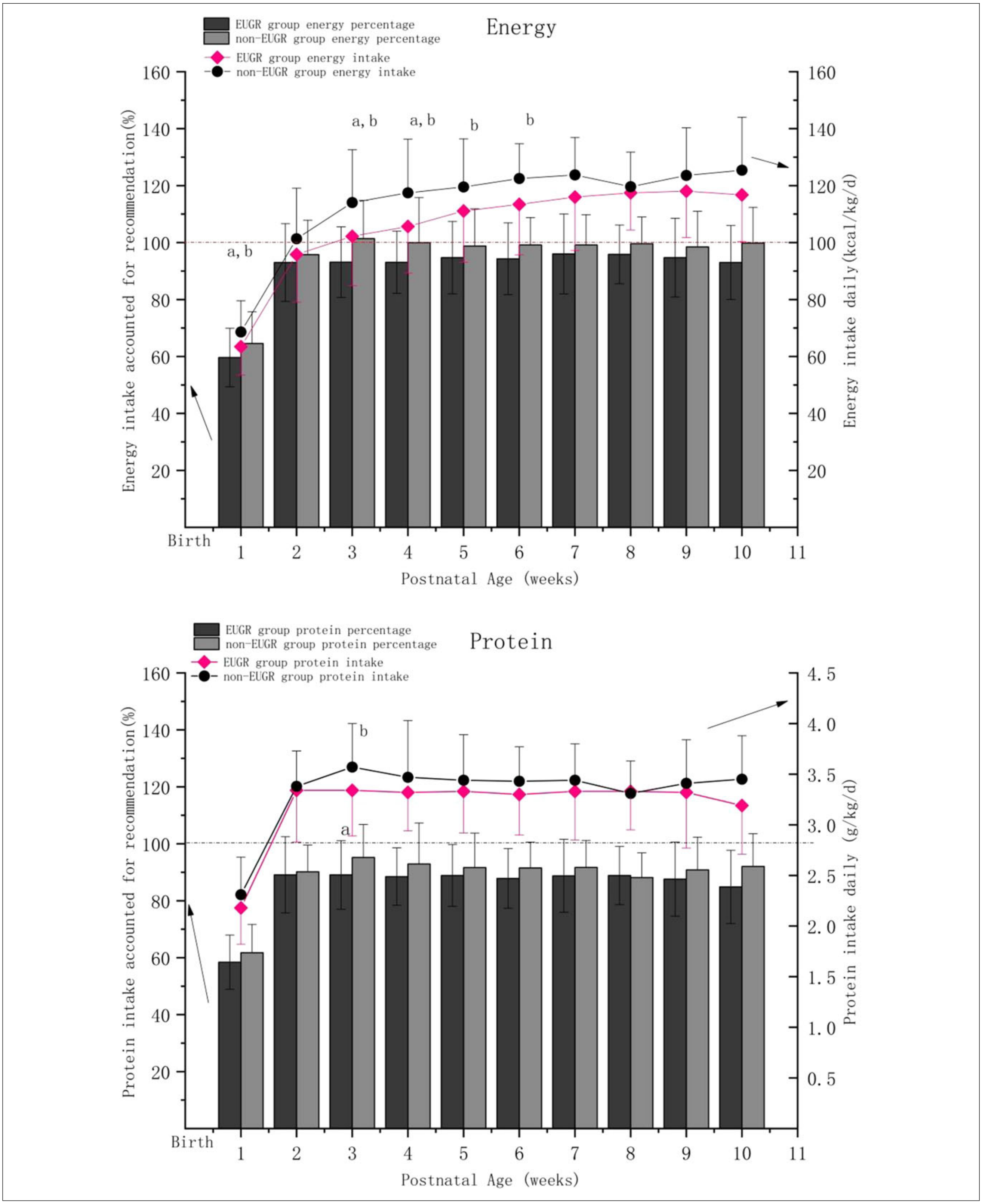

Figure 1. Daily energy and protein intakes and sum of percentages of parenteral and enteral energy and protein intakes in EUGR and non-EUGR groups during hospitalization. Data were analyzed using Student *t*-test. [a]Significant differences in the total percentage of parenteral and enteral energy accounted for recommendations, respectively, between the 2 groups. [b]Differences in daily total energy intakes between the 2 groups. EUGR, extrauterine growth restriction; VLBWI, very low-birth-weight infants.

of EN was significantly higher in the EUGR group (P = .031), and the total energy intake in the first day of full feed was significantly lower in the EUGR group (P = .005). The energy, protein, and lipid intakes were significantly lower in the EUGR group (P < .05).

Goals for parenteral and enteral energy, protein, and lipid intakes were 90 kcal/kg/d for PN and 122.5 kcal/kg/d for EN energy, 3.75 g/kg/d for PN and EN protein, 2 and 6 g/kg/d for PN and EN lipids, respectively.[2,5,12] The amount of lipids intake reached the recommendations after the first week of life, so the results were not presented in this article. The percent of goal, as well as calculated energy and protein intakes, is shown in Figure 1. The sum of the energy and protein percentages was <100% per week. During the first, third, and fourth weeks, the sum of the energy percentages was lower in the EUGR group than in the non-EUGR group (P < .05). The difference in the sum of protein percentages was only during the third week (P < .05).

The daily energy and protein intakes are shown as a line chart on the right y-axis in Figure 1. The differences between the 2 groups were similar to those of the sum of percentages. However, there were significant differences between 2 groups in energy intake during the first and third to sixth weeks (P < .05). The differences between 2 groups were more apparent in the energy intake than that of the sum of the energy percentages.

Even though the differences between the 2 groups were not apparent, the differences in cumulative energy and protein deficits between the EUGR and non-EUGR groups were considerable (Figure 1).

Energy and protein intakes increased rapidly in the 2 groups during the first 2 weeks and leveled off thereafter. However, the cumulative deficits increased during hospitalization. The cumulative energy and protein deficits during the first week and from the third to seventh weeks were higher in the EUGR group than in the non-EUGR group (P < .05). By the end of the 10th week, cumulative energy and protein deficits were 1613.50 ± 629.7 vs 997.97 ± 646.97 kcal/kg/d and 49.51 ± 14.34 vs 41.36 ± 13.59 g/kg/d in the EUGR and non-EUGR groups, respectively. At discharge, the cumulative energy deficit in the 2 groups did not recover.

The changes in weight z-scores weekly from birth to 10 weeks of age are presented in Figure 2 (see also Figure S1). With increasing cumulative energy and protein deficits, the declines of weight z-scores weekly of the 2 groups gradually increased. Weight z-score decreased from −0.89 ± 0.99 at birth to −3.36 ± 1.13 at 10 weeks of age in the EUGR group and from 0.4 ± 0.64 at birth to −0.9 ± 0.53 at 10 weeks of age in the non-EUGR group. The weight z-scores of the 2 groups decreased the most in the first week after birth and were significantly more negative in the non-EUGR group. After that, the declines of weight z-scores were more negative in the EUGR group, especially in the fourth to ninth weeks when there were significant differences between the 2 groups.

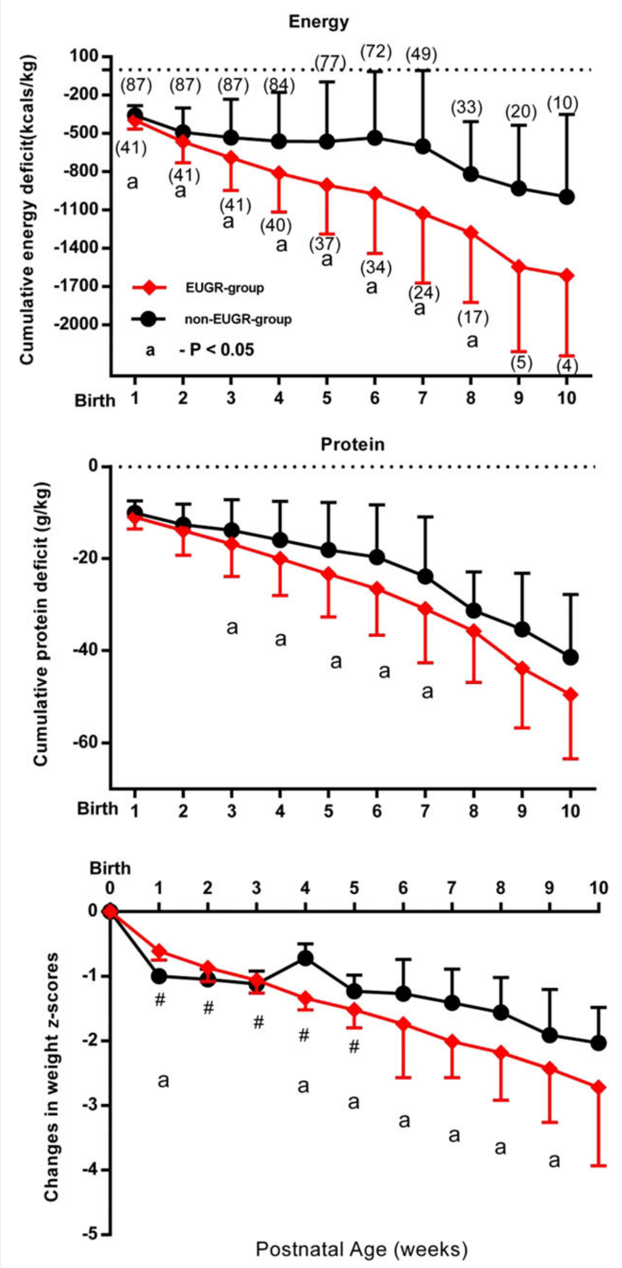

Figure 2. Changes in cumulative nutrient deficits and weight z-scores during the first 10 weeks of life in EUGR and non-EUGR groups. Numbers in enclosed brackets indicate sample size at that time point. [a]Significant differences between the 2 groups as determined by Student t-test. [#]Data were nonnormal presented as quartile. EUGR, extrauterine growth restriction.

After further analysis of multiple linear regression, factors associated with the changes of weight z-scores were cumulative energy deficits (P = .001) and invasive ventilator hours ($P = .038$). Step regression analysis showed that there was a significant negative correlation between the cumulative deficit of energy and changes of weight z-scores ($r = -0.001$; $P < .05$): the energy deficit loss increased by 100 kcal, and the weight z-scores dropped by 0.1 SD.

Discussion

Postnatal growth is a predictor of growth and development in VLBWIs. Adequate nutrition support in the NICU can improve nutrient intake and growth[16,17]; however, reducing the incidence of EUGR is a considerable challenge.[7,8] In this study, the EUGR rate was 68.0% (87/128), which is higher than the EUGR rates in Europe and America.[7,8] The high rates of EUGR in VLBWIs may be attributed to a significant gap between actual and recommended nutrition intake during the first weeks of life.[11]

In this study, the energy and protein intakes were insufficient during hospitalization. The sum of parenteral and enteral energy and protein intakes was <100%, especially of protein intakes in the EUGR group. The deficiencies in energy, protein, and lipid intakes were more prevalent in the first 2 weeks after birth, accounting for 59.6% and 64.6%, 58.4% and 61.7%, and 75.4% and 80.8% in the EUGR and non-EUGR groups, respectively. Similar findings have been previously reported.[11] Even though the differences in percentages between the 2 groups were not considerable, the actual daily intakes of energy and protein, and the cumulative energy and protein deficits were significantly different in the first 8 weeks. In addition, the energy and protein deficits were more evident in the EUGR group than in the non-EUGR group, leading to or exacerbating the occurrence of EUGR in VLBWIs.[11]

It is important to note the energy intake on the first day after the termination of PN. The average energy intake on that day was <100 kcal/kg/d in the EUGR group, which means that the PN support was stopped prematurely in this group. This premature termination of PN leads to insufficient nutrient intake during late hospitalization. This result can also be demonstrated by the weekly cumulative energy and protein deficits during hospital stay.

PN Initiated Late

According to recommendations, PN support with amino acids can be safely administered within 24 hours after birth in VLBWIs.[5,12,18-20] In this study, PN support was initiated within 24 hours of life in 50% of infants with EUGR and within 20 hours in 50% of infants without EUGR. Before PN support, the infusion of glucose without amino acids had been initiated after birth in all VLBWIs. The fluid intake in the first days after birth was restricted, for example, 80–100 mL/kg/d for the first day of life in VLBWIs. Glucose as the only nutrition supplement can hardly meet the nutrition needs of VLDWIs and exacerbates protein catabolism. Glucose and amino acid infusion during the first days of life improves protein balance and increases protein accretion, even at low energy intakes.[21] The administration of parenteral amino acids and lipids improves anabolism and growth.[22] The initial delay in PN support prolonged the time to reach the recommended nutrient intakes, which exacerbated the nutrient deficits in the first weeks of life.

Shortage of Daily PN Support

Different NICUs have different nutrition support practices.[23,24] In our study, the average maximum doses of protein intake in EUGR and non-EUGR groups were 3.15 ± 0.48 and 2.98 ± 0.42 g/kg/d, respectively, and were lower than the recommended levels (3.5–4.0 g/kg/d). Only 20.3% (26/128) of the infants reached recommended levels; 50.8% (65/128) of initial protein intakes were lower than recommended levels. Even though the initial and maximum doses of lipids appeared to be adequate, further analysis revealed that 39.9% (51/128) and 33.6% (43/128) of the initial and maximum doses of lipids, respectively, were less than the recommendations for VLBWIs. Although nutrition support for VLBWIs is based on established guidelines, the initiation of PN is frequently not compliant with current recommendations, especially during the first days of life.[23] The differences between the guidelines and actual PN support may be attributed to the incidence of illnesses and to the medical team. Discussion with experienced pediatricians and nutrition doctors may help to improve the nutrition support of VLBWIs.

PN Terminated Prematurely

According to the guidelines,[12] PN can be terminated when the enteral feeding is >110 kcal/kg/d. In this study, PN was stopped when the enteral feeding reached 100 kcal/kg/d, which was sometimes decided by the attending doctors before calculation of enteral energy and growth rate. The average energy intakes on the first day after PN was terminated were significantly different between the EUGR and non-EUGR groups. In the EUGR group, average energy intake was <100 kcal/kg/d. The average energy intakes on the first day after PN was terminated were significantly different between the EUGR and non-EUGR groups. In the EUGR group, average energy intake was <100 kcal/kg/d, suggesting that PN was terminated prematurely. The enteral energy intakes were <100 and 110 kcal/kg/d for 36.7% (47/128) and 60.2% (77/128) of VLBWIs, respectively. When enteral nutrient intakes cannot meet the requirements for growth and development of VLBWIs, the premature termination of PN will inevitably lead to inadequate nutrient intakes. Therefore, inadequate nutrient intakes may occur during a later period of hospital stay and not just during the first few weeks of hospitalization. More attention should be paid to the insufficient nutrient intakes during the entire hospital stay. It is important for nutritionists and pediatricians to perform a comprehensive nutrient assessment to determine whether to terminate PN.

Excessive EN Interruption

The interruption rate of EN was significantly higher in the EUGR group. The interruption rate of EN in this study was 21.1%, which was lower than that reported by Lima et al[25] (29.9%). EN interruption may be caused by avoidable or unavoidable factors, for example, feeding intolerance (abdominal distension and gastric retention), necrotizing enterocolitis (NEC), surgeries (tracheal intubation and preoperative fasting of retinopathy of prematurity), and examinations (ultrasound and fundus examination).[26] The diagnosis at discharge showed that the incidence rates of upper gastrointestinal bleeding, feeding intolerance, and NEC were only 7.0% (9/128), 2.3% (3/128), and 3.1% (4/128), respectively, which suggests that there is an excessive interruption of EN in this population. Currently, there is no standard protocol to minimize EN interruptions. Further research on EN interruptions is required to establish a reasonable and effective protocol for EN interruptions.

Strengths and Limitations

Actual nutrition intake and the problems existing in the process of nutrition support of this population still need more in-depth study. The research data about this part in the global articles are relatively blank. This article can provide data reference of this population to domestic and foreign researchers, and help to improve the nutrition support in the future.

There are 2 main weaknesses in this study. One is that this is a single-center, retrospective study with a small sample size. Another is that SGA infants are included in this study, and in this study we found that SGA infants may have an influence on the results. Although we have carefully searched and collected data, a multicenter observational study is urgently needed.

Conclusions

There may be other nutrition support problems that have not been specifically addressed in this study. What we should know is that it takes time for VLBWIs to reach the recommended dietary intakes, and that they are rarely maintained throughout hospitalization.[11] The nutrition support was designed to meet needs for maintenance and normal growth as opposed to excessive catch-up growth. The cumulative energy and protein deficits increase on a weekly basis during hospitalization, which inevitably increases the adverse effects of excessive catch-up growth in the future.[27,28] It is important to provide stable and adequate nutrients not only in the first weeks of life, but throughout the hospital, and even when discharged home. The implementation of a program with potential improvement of nutrition practices may promote a more adequate supply of nutrients, reduce EUGR, and decrease comorbidities in VLBWIs.[17,24,29,30]

Statement of Authorship

F. Hu, Q. Tang, and W. Cai contributed to the conception and design of the research; Y. Wang, J. Wu, and H. Ruan contributed to the design of the research; F. Hu, Q. Tang, J. Wu, and H. Ruan contributed to acquisition, analysis, and interpretation of the data; Q. Tang, Y. Wang, L. Lu, and Y. Tao contributed to analysis of the data; F. Hu and Q. Tang drafted the manuscript. All authors critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors 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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