ORIGINAL

Nutritional Care of Preterm Infants: from Global Guidelines to Local Practice

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ABSTRACT *Background.* Meeting the nutritional needs of preterm infants represents a huge challenge. According to previous studies, higher intakes of protein and energy in the first week of life are linked to improved neurodevelopmental outcomes. However, whether these global guidelines can be successfully implemented at the local level requires further study. *Methods*. This is a retrospective cohort study, for the period from Oct 2016 through Nov 2017. All participating subjects reached 75% of the nutritional targets within one week of birth as the standard of care. But given the clinical condition constraints, they almost inadequate nutrition in the first weeks of life. We conducted a trial involving 122 preterm divided into four groups to determine the most appropriate nutritional strategy: HCHP (more calories and higher protein intake); LCLP (fewer calories and lower protein intake); HCLP (more calories and lower protein intake) and LCHP (higher protein intake and fewer calories). *Results*. Higher energy intake in the first week after birth was related to significant decreases in the average duration of hospitalization ($p<0.05$) and significant weight gain ($p<0.05$). Adequate caloric intake is more important than high protein intake. Furthermore, early aggressive nutritional strategy may help to decreases in length of ICU stay. (HCLP versus LCLP group, odds ratio 0.022 [95% CI 0.003-0.189]). *Conclusion*. Based on the results of this study, we determined the optimal nutritional support for preterm infants. Protein is an important factor in developmental outcomes and can be used most efficiently when associated with adequate caloric intake.

Keywords: Nutritional Requirements; Nutritional Support; Nutrition Therapy; Premature Infant.

INTRODUCTION

Early aggressive nutrition is essential for preterm infant growth and immunity. In preterm infants, poor nutrition is associated with poor head growth and persistent small head size results in poor psychomotor and mental skills and high rates of cerebral palsy and autism (1). Preterm infants are at a higher risk of growth and developmental disabilities compared to their full-term counterparts. Early administration of optimal nutrition to preterm infants lowers the risk of adverse health outcomes and improves cognition in adulthood (2). Recommendations for the nutritional management of preterm infants by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the American Academy of Pediatrics (AAP) and the Taiwan Society of Neonatology (TSN) Committee on Nutrition include higher intakes of protein and energy in the first week of life, which have been linked to improved neurodevelopmental outcomes (3). Amino acids and proteins are key factors for growth. Current recommendations are designed to provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age (4). The prevailing nutritional practices for preterm infants include energy requirements of 110~130 kcal/kg/day and protein intake of 3.5~4.5 g/kg/day (5). Various disciplines have contributed specialized expertise to the identification of potentially better practices (6). Although the Committee on Nutrition of ESPGHAN announced appropriate recommendations in 2007, it was considered necessary to review them (8). The updated guidelines are consistent with, but not completely identical to, the major recommendations prior to 2010. However, whether these global guidelines can be successfully implemented on a local level requires further study. Differences in medical care and social factors among countries may limit the generalizability of global guidelines (13). The aim of this study is to review and discuss the manner in which the postnatal growth of preterm infants is monitored in neonatal intensive care units (NICUs) and to investigate whether growth and clinical outcomes are associated with the adequacy of postnatal nutrient intake.

METHODS

This was a retrospective cohort study, conducted for the period from Oct 2016 to the end of Nov 2017, on preterms admitted to the NICU at local medical

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center and who met the criteria for inclusion. Those who died within 7 days were excluded, of which there were two. Therefore, mortality rate was not considered an indicator. In addition, infants who remained in the hospital at the end of the study period were excluded (Figure 1). All participating subjects reached 75% of the nutritional targets within one week of birth as the standard of care. Due to clinical constraints, almost all received inadequate nutrition in the first weeks of life. The nutritional protocol was to start parenteral nutrition on day 1 and first enteral feed as soon as possible after birth. Continued provision of appropriate nutrition (fortified human milk or premature formula) is important throughout the hospitalization period. Subjects were assigned to one of four groups based on number of calories and amount of protein ingested daily during the first seven days of admission to NICU: high calorie intake group (HCLP) which received more than 75% of the energy needs (90 kcal/kg/day); high protein intake group (LCHP) which received at least 75% of the protein requirement (3 g/kg/day); high calorie and protein intake group (HCHP) which received at least 90 kcal/kg/day with 3 g/kg/day of protein and low calorie and protein intake group (LCLP group) which received less than 90 kcal/kg/day and less than 3 g/kg/day of protein. Perinatal and neonatal data were retrieved from medical records (Figure 1). Weight gain and blood biochemical values were collected after two weeks of nutritional support. Complication rates and lengths of hospital stay were also analyzed. Finally, we explored the impact of nutritional support on the clinical outcomes of preterm infants. This study was conducted according to the guidelines of the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Board of Chung Shan Medical University Hospital (CSMUH IRB No: CS-18256).

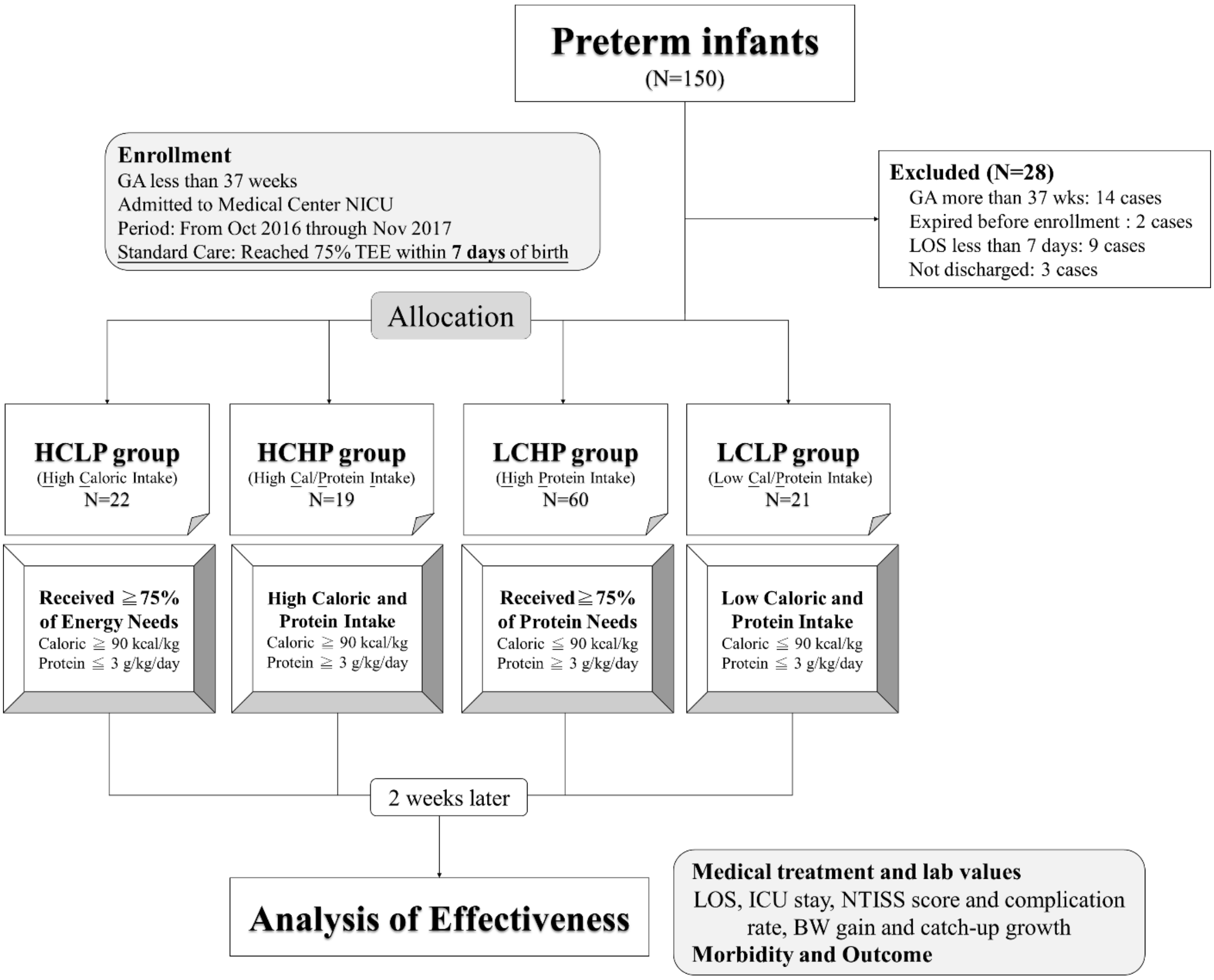

Figure 1. Enrollment flow chart and study protocol

Characteristics

The Neonatal Therapeutic Intervention Scoring System (NTISS) was used to indicate disease severity in neonates requiring intensive care (14). NTISS scores were calculated on the first day and at 7-14 days after admission. The predictive power for clinical outcomes included the average duration of hospitalization (length of stay, LOS) and number of days in ICU. Furthermore, preterm infants can suffer from morbidities such as patent ductus arteriosus

(PDA), respiratory distress syndrome (RDS) above grade II, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), metabolic bone disease, hypoxic ischemic encephalopathy (HIE), congenital intestinal malrotation and spontaneous intestinal perforation (SIP) (15). Neonatal morbidities were diagnosed by pediatric specialist and retrieved from medical records. Complications in this study were defined as the combination of more than two of these morbidities. Preterm infants received surgical intervention including PDA ligation, external ventricular drainage (EVD)/ventriculoperitoneal shunt (V-P shunt) procedure, photoligulation, inguinal hernia repair and enterostomy.

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQRs) and reported as 25th-75th percentiles. Categorical variable comparisons were performed with Pearson chi-square test or Fisher's exact test. To determine whether the effect of the intervention on the end points was influenced by baseline risk factors, p values for interactions were calculated with one-way ANOVA and post hoc analysis with Scheffé test with threshold for significance of interaction set at $p<0.05$. For continuous parameters in non-normal distribution, Kruskal-Wallis H test was used when the assumptions of one-way ANOVA were not met. We further performed Mann-Whitney U test to compare the differences between two groups. As the group with the highest intakes was comprised of infants of the highest gestational age (GA) and birth body weight (BBW), confounders were GA and BBW. Following initial analysis, logistic regression analysis was performed for variables without statistically significant difference. Furthermore, we adjusted for the confounders GA and BBW during the nutritional treatment period and clinical outcome. Logistic regression was applied to the baseline characteristics and clinical outcome. All analyses were performed using PASW Statistics 18, version 18.0.0 (formerly SPSS Statistics).

RESULTS

A total of 122 preterm infants of less than 37 weeks' gestational age were eligible for this study. The basic characteristics of these infants are shown in Table 1. Infants in the LCLP group had lower GA, lower BBW, and lower Apgar scores at 1 minute and 5 minutes when compared with infants in the HCLP group (all $p< 0.05$). On post hoc analysis with Scheffé test, there were statistically significant differences in GA between the HCLP and LCHP groups and the HCLP and LCLP groups. Similarly, there were statistically significant differences in BBW and Apgar score at 1 minute. We performed logistic regression analysis with the significant variables BBW and GA. After adjusting for significant factors, there were no significant differences between groups at baseline as presented in Table 1.

In addition, there were no associations with laboratory data after 2 weeks of nutritional support, such as hemoglobin, white blood cell count and platelet count. Similar results were found for electrolyte balance (data not shown). Median C-reactive protein levels were within normal range with decreased inflammation in all groups at 2 weeks. Unfortunately, information about nutritional status and possible indexes to be applied to organ function maturity was limited. Due to insufficient data on serum albumin, alkaline phosphatase, bilirubin level, γ-glutamyltransferase and creatine kinase, these could not be analyzed.

Adequate nutritional support was associated with improved growth and clinical outcomes and less extrauterine growth retardation (EUGR) (Table 2). High energy with low protein intake during the first week after birth was associated with significant decreases in the average duration of hospitalization and length of ICU stay (HCLP versus LCLP group both $p<0.01$, respectively). Higher energy with higher protein intake was only associated with significant decreases in length of ICU stay (Figure 3), indicating an excellent predictive marker for clinical outcome. Additionally, HCLP group showed significantly improved weight gain at 2 weeks when compared with LCHP group and LCLP group ($p<0.05$, Table 2).

Although administration of optimal nutrition resulted in lower risk of more than two preterm complications and surgical intervention for morbidities (Adjusted $p>0.05$), there were significant differences in ICU stay between HCLP versus LCLP groups and HCHP versus LCLP groups (Figure 3). For HCLP versus LCLP group, odds ratio was 0.022 [95% CI 0.003-0.189], $p=0.001$ and for HCHP versus LCLP group, odds ratio was 0.044 [95% CI 0.006-0.33], $p=0.002$. Moreover, LCLP group showed significantly increased LOS (HCLP versus LCLP group, odds ratio 0.022 [95% CI 0.002-0.267], $p=0.003$).

DISCUSSION

Providing more than 75% of the nutritional needs to preterm infants within 7 days of birth can improve clinical prognosis. Protein administration is more effective when number of calories is adequate. Although survival of premature infants has improved, there is a continuing need to develop and implement strategies for reducing the potentially lethal complications of premature birth (16). Early aggressive nutritional enteral and parenteral support may help to improve growth and developmental outcomes in preterm newborn low birth weight (LBW) infants (12). In preterm infants, poor postnatal growth is associated with adverse neurocognitive outcomes. Conversely, rapid postnatal growth is considered a risk factor for future development of metabolic diseases (17). Therefore, sufficient nutritional support and optimal nutritional delivery are essential. Protein-energy balance studies of preterm infants have provided data to guide recommendations for protein-energy intakes for specific short-term goals (18). Nevertheless, from the results of our study on the relevance of energy it is particularly important to promote protein balance at lower energy intakes, as amino acids are increasingly used for oxidative metabolism when non-protein energy is limited. Regardless of protein intake, however, nutritional balance requires increased energy intake. A reasonable explanation for no associations with laboratory data in this study is that the biochemical values of premature infants are monitored daily and corrected immediately.

Table 1. Baseline characteristics of patients at enrollment

Characteristics$^{\alpha}$		HCLP 90kcal	HCHP 90kcal+3g	LCHP 3g	LCLP None	p value$^{\beta}$	Adjusted p^{γ}
Number		22 (18.1)	19 (15.6)	60 (49.2)	21 (17.2)	-	-
Male		12 (54.5)	7 (36.8)	35 (58.3)	14 (66.7)	0.268	-
GA (wk)		35.86 [ab] (34.1-36.3)	35 [c] (33.9-35.4)	33.07 [a] (30.3-34.3)	33.86 [bc] (27.4-34.9)	<0.01	0.119
BL (cm)		45.3 (42-48.3)	45.5 (42-47.5)	42 (39-46)	42 (35.3-47.5)	0.027	0.121
BBW (kg)		2.300 [de] (1.863-2.550)	2.020 (1.730-2.269)	1.756 [d] (1.301-2.066)	1.758 [e] (0.975-2.252)	<0.05	0.66
Apgar Score	1 min	8 (7-8.25) [fg]	8 (7-8) [h]	7 (6-8) [f]	6 (5-7.5) [gh]	<0.01	0.138
	5 min	9 (9-9) [i]	9 (9-9)	9 (7-9)	8 (7-9) [i]	<0.01	0.439

$^{\alpha}$ *Continuous variables are presented as median (IQR) and categorical variables as n (%)*
$^{\beta}$ *The p values are from Pearson chi-square test for categorical variables and from one way ANOVA or Kruskal-Wallis test for continuous variables.*
$^{\gamma}$ *Adjusted p values are from binary logistic regression analysis after adjusting for significant factors. (Confounding variables: BBW, GA)*
* *The same English symbols indicate significant difference*

Table 2. Clinical outcomes of each group

Intervention Period	Prognosis assessment					
	Nutritional therapy groups				p-value	Adjusted p
	HCLP	HCHP	LCHP	LCLP		
Actual Calories (kcal/kg BW)	104.6 (99-113.5)	101.5 (92.5-117.8)	74.2 (66.2-79)	57 (51.7-71.7)	<0.01	-
Actual Protein (g/kg BW)	2.56 (2.29-2.67)	3.67 (3.38-4.09)	3.74 (3.46-4.11)	2.83 (2.52-2.95)	<0.01	-
LOS (days)	14.5 [a] (12.8-21.5)	28 (14-37)	39.5 (27.3-74.3)	61 [a] (30-97.5)	**<0.01**	**0.025**
ICU stay (days)	7.5 [b] (5-12)	12 [c] (7-21)	23 (15.3-51.5)	46 [bc] (17-71.5)	**<0.01**	**<0.01**
BW gain (gm)	290 (171-357)	188.5 (65.8-258.3)	91.5 (36.8-155.8)	101 (36-179.5)	**<0.01**	**0.015**
NTISS score (after 7~14 days)	8 (5-10.5)	9 (7-9)	9.5 (7-15)	10 (7-21.3)	0.087	-
Complications	3 (14)	5 (26)	28 (47)	14 (67)	**<0.01**	0.287
Surgery	0 (0)	2 (11)	13 (22)	10 (48)	**<0.01**	0.437

* *Continuous variables are presented as median (IQR) and categorical variables as n (%)*
* *The same English symbols indicate significant difference*
* *Adjusted p values are from binary logistic regression analysis after adjusting for significant factors. (Confounding variables: BBW, GA)*

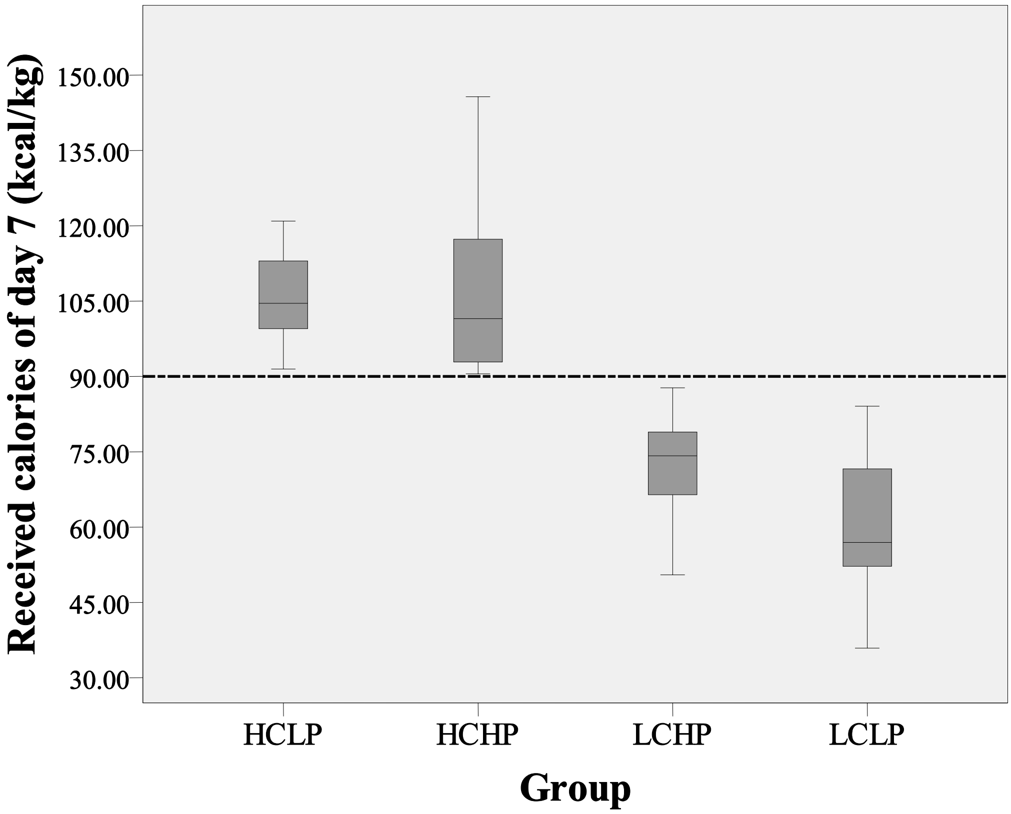

Figure 2a. Actual caloric intakes of each group. There were significant increases in HCLP and HCHP group when compared with LCHP and LCLP groups.

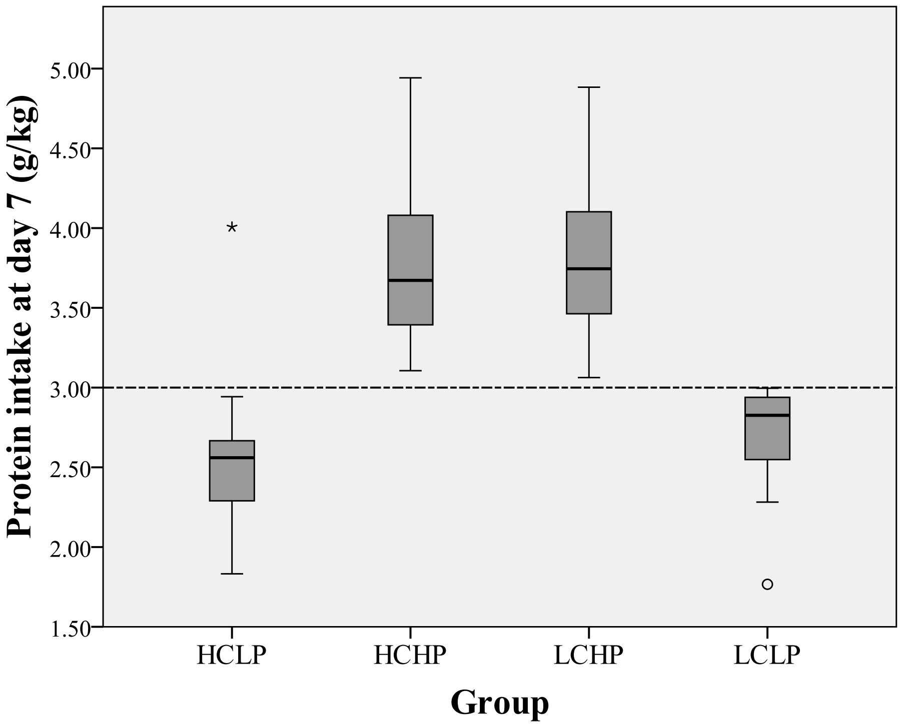

Figure 2b. Actual protein intakes of each group. There were significant increases in HCHP and LCHP group when compared with HCLP and LCLP groups.

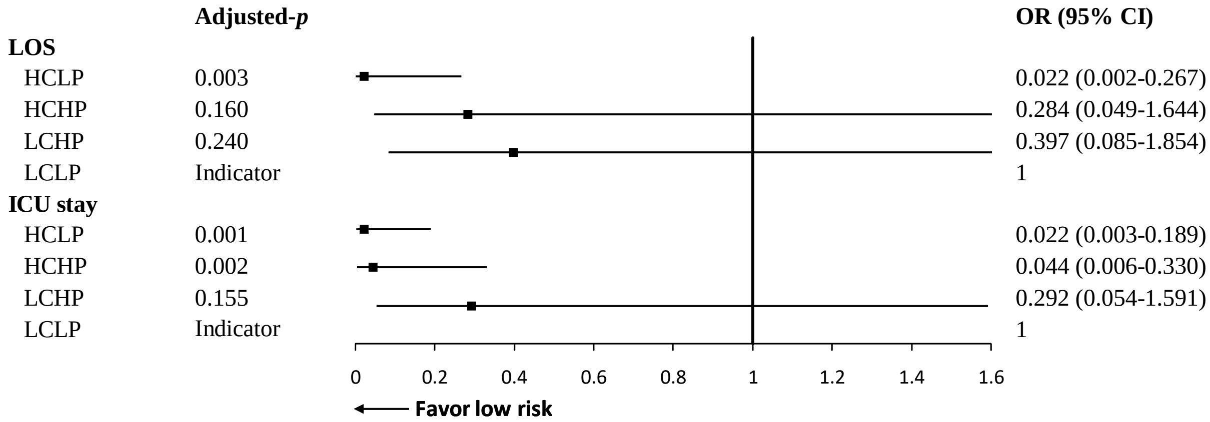

Figure 3. The relevance of this experiment. HCLP group showed significant improvement in odds ratios of LOS and ICU stays when compared with LCLP groups.

Previous studies have suggested that increasing energy intake in the face of static protein intake should be avoided in the first week of life (19). As there is often a gap between global guidelines and the results of clinical practice, NICUs should develop their own methods of nutritional support for preterm infants suited to local conditions and actual patient needs. Our study of a local practice revealed the optimal nutritional support strategy for preterm infants. Greater energy and lipid intake predict increased total brain and basal nuclei volumes over the course of neonatal care to term-equivalent age (20). Evidence linking postnatal weight gain to later adiposity and other cardiovascular disease risk factors in preterm infants is limited (17). In our study, more than 90 kcal/kg/day with or without 3 g/kg/day protein was associated with sufficient weight gain (> 150 g/week). Consistent with the findings of a previous study, emphasis should be on providing optimal energy and protein during the first week following birth (21).

A previous study proposed that infants weighing ≥1250 g be fed three times hourly and those weighing <1250 g be fed two times hourly (22). The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) recommend that enteral feeding protocols be designed and implemented to increase the overall percentage of goal calories provided. For instance, volume-based feeding protocol or top-down multi-strategy protocol should be considered (23). Protocols in which 24-hour or daily volumes are targeted instead of hourly rates have been shown to be successful in increasing the overall percentage of goal energy provided. Consequently, daily volumes may be applied to preterm feeding protocol for catch-up growth and early aggressive nutritional support.

The major limitation of this study is that enteral nutrition and parenteral nutrition were not calculated separately, although each has different requirements. We started parenteral nutrition on day 1 and first enteral feed as soon as possible after birth. However, their effects could not be differentiated. Correspondingly, determining simple causes of clinical outcome when multiple causes may play a role can be difficult and subjective. We used regression statistics to minimize bias in determining variables, but with uncertain validity. From observational studies there are consistent positive associations between nutritional support and clinical outcomes. However, there is limited evidence from intervention studies. Given the above constraints, further studies are needed to clarify the effects of early nutritional intervention on preterm infants.

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