Original Article

Analysis of nutritional status of preterm infants at early life

Guanming Li[1], Airun Zhang[1], Hanni Lin[1], Min Wang[1], Xiaoyi Fang[1], Silan Yang[2], Niyang Lin[2]

[1]Department of Neonatology, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, China; [2]Department of Neonatology, First Affiliated Hospital, Shantou University Medical College, Shantou 515041, China

Contributions: (I) Conception and design: X Fang, N Lin; (II) Administrative support: None; (III) Provision of study materials or patients: G Li, A Zhang, H Lin, S Yang, X Fang; (IV) Collection and assembly of data: G Li, A Zhang, H Lin, S Yang, X Fang; (V) Data analysis and interpretation: X Fang, G Li, A Zhang, H Lin, M Wang, S Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiaoyi Fang. Department of Neonatology, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen 518107, China. Email: judyfangxy@126.com.

Background: A rational energy and nutrient intake is important for the physical development of preterm infants to prevent extrauterine growth retardation (EUGR).

Methods: Data of feeding strategies were recorded from 141 preterm infants while they were hospitalized in a neonatal intensive care unit (NICU) and during follow-up until 3 months after discharge. Weight gain velocity, the period of returning to the birth weight, and achieving the reference dietary intakes (RDIs) were analyzed. The incidence of intrauterine growth retardation (IUGR) and EUGR were compared and the possible underlying reasons were explored.

Results: The mean period of returning to birth weight was 13.2 days. The average weight gain after achieving birth weight was 16.7g/(kg·d). The mean period of reaching RDIs was 10.6 days. The incidence of EUGR at discharge (46.6%) was higher than that of IUGR at birth (17.7%) ($P<0.01$). The incidence of EUGR in infants with gestational age (GA) <34 weeks was higher than those ≥34 weeks ($P<0.05$). The incidence of EUGR at the 3rd month after discharge was similar to that at discharge ($P>0.05$). There was no significant difference in the incidence of EUGR at the 3rd month after discharge between the preterm infants with GA <34 weeks and ≥34 weeks ($P>0.05$). The incidence of EUGR was lower in preterm infants fed by breast milk with human milk fortifier (HMF) or post-discharge formula (PDF) compared with those fed by breast milk or term formula milk ($P<0.05$).

Conclusions: EUGR is not rare in preterm infants, especially those with small GA during the early stage of life, which is difficult to be improved within a short period of time. After discharge, feeding with fortified breast milk or PDF is more suitable than feeding with the pure breast milk or term formula milk to prevent EUGR in preterm infants.

Keywords: Extrauterine growth retardation (EUGR); preterm infants; nutrients; growth velocity

Received: 15 March 2019; Accepted: 27 March 2019; Published: 12 April 2019.
doi: 10.21037/dmr.2019.03.04
View this article at: http://dx.doi.org/10.21037/dmr.2019.03.04

Introduction

Since the improvement in neonatal intensive care, newborns with an increasingly small gestational age (GA) and very or extremely low birth weight have survived with less complications and sequela. Appropriate nutritional support during early life is essential to ensure the proper growth and development of the infants. Unfortunately, despite efforts of improving nutrition management, especially feeding strategies, many preterm infants still do not receive adequate nutritional support due to various factors, which might result in extrauterine growth retardation (EUGR). In this study, the feeding practice and weight gain of preterm infants were evaluated during hospitalization and 3 months after discharge.

Methods

Subjects

Preterm newborns were sampled from neonates admitted to NICU of the First Affiliated Hospital of Shantou University Medical College from January 2014 to January 2016. In total, 141 preterm infants who were born before 37 weeks, hospitalized within 24 hours after birth, and participated in follow-up clinics until 3 months after discharge, were included. Infants with congenital malformations or metabolic diseases were excluded. Seventy-eight males and 63 females were enrolled, among whom 3 (2.13%) were extremely low birth weight infants (ELBWI), 43 (30.50%) were very low birth weight infants (VLBWI), 85 (60.28%) were low birth weight infants (LBWI), and 10 (7.09%) were normal birth weight infants (NBWI). The GAs varied from 27 to 36 weeks with a median of 31^{+6} weeks. Hospitalization days ranged from 4 to 66 days with a median of 21.5 (10.1, 44.8) days. Weights at discharge varied from 1,400 to 4,220 g with a median of 2,463.7 (1,809.7, 2,201.4) g. As it relates to the primary diseases, there were 78 cases of neonatal respiratory distress syndrome, 25 cases of infectious pneumonia, 10 cases of aspiration pneumonia, 10 cases of asphyxia, 9 cases of intrauterine infection, and 9 cases of pathological jaundice. As this was a retrospective study, informed consent was exempt from approval by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College.

Nutrition practices

Nutritional strategies mainly followed "Guide for feeding preterm/low-birth-weight infants" recommended by the Chinese Society of Pediatrics (1). Enteral feeding should be started as soon as possible for the infants without congenital digestive tract malformations and critical medical conditions. The trophic feeds were started within 12 hours after birth to those infants whose birth weight was larger than 1,000 g with relatively stable vital signs, and it was delayed to 24–48 hours after birth in those who had severe perinatal asphyxia and extremely low birth weight. Breast milk was the first choice of feeding regimen. As the volume of breast milk was more than 100 mL/kg, human milk fortifier (HMF) was initially added semi-enhanced and then fully-enhanced if tolerated. If there was no or not enough breast milk, preterm formula milk was used. Trophic feeds started from 12 mL/(kg·d). If the infants could tolerate it, nutritional feeds were gradually introduced from 15–20 to 150–180 mL/(kg·d). The total or partial parenteral nutrition strategy was based on the "Guide for clinical application of nutrition support in critical neonates in China" (2). The types of milk after discharge included pure breast milk, breast milk with HMF, post-discharge formula (PDF), and term formula milk.

Data collection

The clinical data, including daily weight gain, initiation time of enteral nutrition, the period of returning to birth weight, the period of achieving the reference dietary intakes (RDIs) of 120 kcal/(kg·d), etc., were collected. The weight, length, and head circumference (HC) were recorded weekly during hospitalization and at the 1st week, 1st month, 2nd month, and 3rd month after discharge during follow-up. The evaluation of growth was based on Fenton Growth Chart 2013 (3) or the Child Growth Chart of Nine Cities in China 2005 (4) before or after corrected GA of 40 weeks. IUGR was defined as any anthropometric value, including weight, length or HC, below the 10th percentile at birth while EUGR was defined as an anthropometric value below the 10th percentile of corrected age. The definition of pathological weight loss was the following: the weight loss was more than 10% of birth weight, or body weight did not return to birth weight within 10 days after birth.

Statistical analysis

SPSS for Windows 13.0 statistical analysis software was used for statistical analysis, *t* test was used for comparison of quantitative data, χ^2 test was used to compare rate, and nonparametric rank-sum test was used to analyze the skew distribution data. $P<0.05$ was considered as statistically significant.

Results

Feeding and growth during hospitalization

The initiation time of nutritional feeds ranged from 1 to 20 d after birth with a median of 4.3 d. The period of achieving RDIs was 3 to 30 d with a median of 10.6 d. The underlying reasons for feeding delay might involve gastric retention (46.10%), abdominal distention (25.53%), coffee-ground like (19.15%) or biliary (9.22%) vomiting, or gastric aspiration. Among the 141 preterm infants, 103 had physiological weight loss and 38 had pathological weight

Table 1 Comparison of feeding and growth between preterm infants with different GA during hospitalization

Variable	GA (weeks)		P value
	<34 (N=48)	≥34 (N=93)	
Initiation time of nutritional feeds (d)	7.43±4.11	2.63±1.27	<0.05
Period of achieving BW (d)	15.50±6.23	10.68±4.98	<0.05
Period of achieving RDIs (d)	15.69±8.83	7.92±4.56	<0.05
Weight gain [g/(kg·d)]	18.92±6.55	14.50±9.50	>0.05
Cases of IUGR (%)	7 (14.6)	18 (19.4)	>0.05
Cases of EUGR (%)	31 (64.6)	34 (36.6)	<0.05

The data are presented as mean ± SD or n (%). GA, gestational age; BW, birth weight; RDIs, reference dietary intakes; IUGR, intrauterine growth retardation; EUGR, extrauterine growth retardation.

Table 2 Comparison of growth status between preterm infants with different GA 3 months after discharge

Variable	GA (weeks)		P value
	<34	≥34	
Cases	48	93	–
Cases of EUGR at the 3rd month after discharge, n (%)	25 (52.1%)	38 (40.9%)	>0.05
Average weight gain (g/mon)	539.7	588.7	>0.05

GA, gestational age; EUGR, extrauterine growth retardation.

loss. A total of 124 infants had achieved birth weight before discharge. The period of returning to the birth weight was 11–20 d with a median of 13.2 d. The velocity of weight gain after achieving birth weight was 2–38 g/(kg·d), with a median of 16.7 g/(kg·d). The growth velocity of the length and head circumference were 0.2–1.7 and 0–1.4 cm/week, with a median of 1.0 and 0.8 cm/week, respectively. There were 25 cases (17.7%) of IUGR. However, there were 65 cases (46.1%) of EUGR at discharge. The incidence of EUGR was significantly higher than that of IUGR (χ^2=6.68, P<0.01). There were differences in feeding regimen and weight gain between preterm infants born before or after 34 weeks of gestation. The comparison is shown in *Table 1*. The velocity of weight gain and incidence of IUGR were similar between the two groups. Feeding delay was more serious and the incidence of EUGR was higher in preterm infants born before 34 weeks of gestation than those born after 34 weeks of gestation.

Feeding and growth after discharge

After discharge, the preterm infants were fed by different kinds of milk according to the parents' choice and doctors' recommendation. At the 3rd month after discharge, the incidence of EUGR was 44.7% (63/141), which was similar to that at discharge (P>0.05). The incidence of EUGR and the growth velocity were not significantly different between the preterm infants born before and after 34 weeks of gestation (P>0.05) (*Table 2*). The differences of incidence of EUGR and growth velocity among infants under different feeding regimens were statistically significant (P<0.05). Infants fed by fortified breast milk or breast milk with PDF had less EUGR and better weight gain compared with those fed by pure breast milk or term formula milk (*Table 3*).

Discussion

Optimal nutrition support for preterm infants especially ELBWI/VLBWI is essential to promote neonatal overall survival and a better long-term outcome. Evidence from randomized controlled clinical trials showed that enhanced nutrient intakes within the first few weeks in preterm infants benefited cognitive function in adolescence by changing brain structure (5,6). Therefore, preterm infants have been reasonably proposed to achieve a growth velocity as close as possible to the normal intrauterine growth of the same

Table 3 Comparison of development status among preterm infants fed by different kinds of formula

Variable	Types of formula					P value
	Breast milk	Breast milk + HMF and breast milk + PDF	Breast milk + term formula	PDF	Term formula	
Cases	17	16 (4 and 12)	23	31	54	–
Cases of EUGR at the 3rd month after discharge, n (%)	5 (29.4%)#	4 (1 and 3) (25%)•* ★◇	10 (43.5%)#	11 (35.5%)#	22 (40.7%)#	<0.05
Average weight gain (g/mon)	553.6#	626.6•*◇	581.7#	600	541.6#	<0.05

•, compared with breast milk group P<0.05; #, compared with breast milk + HMF and breast milk + PDF group P<0.05; *, compared with breast milk + term formula group P<0.05; ★, compared with PDF group P<0.05; ◇, compared with term formula group P<0.05.

GA (7). Early initiation and rapid increase of enteral feeding was encouraged to maintain proper growth, promote maturity of gastrointestinal function, and achieve an RDI of 120 kcal/(kg·d) in preterm infants (8-10). Yet, despite substantial effort, a vast proportion of the preterm infants fail to gain the proper growth rate, or even fall below the 10th percentile, which means EUGR.

Universally, EUGR in preterm infants is not rare. Clark *et al.* conducted a retrospective study on 24,371 preterm infants with GAs of 23–34 weeks and evaluated the incidence of growth restriction at discharge by weight, length, and head circumference, which were 28%, 34%, and 16% respectively (11). The pediatric collaboration group of the Chinese Society of Parenteral and Enteral Nutrition analyzed the data of preterm infants from 10 hospitals and found that the incidence of IUGR and EUGR at discharge was 27.3% and 60.1% respectively (12). The incidences of IUGR and EUGR at discharge in our study were 17.7% and 46.1% respectively. The EUGR incidence in infants born before 34 weeks of gestation was significantly higher than those born after 34 weeks of gestation, which indicated that infants with smaller GA were more prone to get EUGR. IUGR is associated with gene expression and hereditary factors. A number of EUGR cases were a continuation of IUGR. Nutritional factors could regulate gene expression through epigenetic modification regarding the correlation between methylation and the protein and lipid intake. Imprinting Centre 1 (IC1) is the popularly studied gene region. A pilot study found that a reduction of nutritional intake was negatively feedbacked to increase IC1 methylation, causing an increase of insulin-like growth factor (IGF)-2 expression in order to promote a catch-up growth and to prevent EUGR (13). Even though these gene expressions were reversible with abundant nutrition supplementation (14), there were still a proportion of infants with IUGR that persisted to EUGR. On the other hand, the smaller the GA was, the more immature the gastrointestinal function was, the longer the gastric emptying time and poorer the intestinal peristalsis they had, and the greater the likelihood was of developing feeding intolerance. As indicated by our study, feeding intolerance presenting as gastric retention and abdominal distension was the main reason for postponing nutritional feeds. Inadequate enteral feeds rarely met increasing metabolic demands and nutritional needs of preterm infants, which resulted in malnutrition and failure to thrill. Other intricate factors, including regional, ethical, and traditional factors may also contribute to EUGR, perhaps through interactions with genetics and epigenetics. However, the molecular mechanisms need further investigations.

The growth velocity was ideally 10–20 g/(kg·d). Bloom *et al.* analyzed the weight growth of 1,995 preterm infants with birth weight of 401–1,500 g within 28 days after birth and found that the mean weight gain velocity was only 8.7±5.0 g/d in the slow-growth group (834 cases) and 12.7±6.0 g/d in the fast-growth group (1,161 cases) (15). In our study, preterm infants had a weight gain velocity of 2–38 g/(kg·d) after returning to birth weight, with an average growth gain of 16.7 g/(kg·d). The preterm infants with GA <34 weeks had delayed nutritional feeds due to various medical conditions and the period of returning to birth weight and achieving RDIs was prolonged. However, after returning to birth weight, they had a similar weight gain velocity to the preterm infants with GA ≥34 weeks, perhaps due to more aggressive parenteral nutrition support. These results should be scrutinized under light of the study's small sample size, which might lead to the bias.

The incidence of EUGR in the 3rd month after discharge was not significantly improved compared with that at discharge, which may be related to inappropriate feeding

strategy after discharge. Several clinical randomized controlled trials suggested that the premature infants fed with nutritionally enhanced formula, including PDF and HMF, after discharge, were more conducive to achieving catch-up growth than those fed by breast milk (16,17). Milk fortifier was recommended for preterm infants to enhance the nutrient supplement. However, the fortifier introducing rate was low in this study. A vast number of premature infants after discharge were still fed by pure breast milk or term formula milk, leading to high incidence of EUGR.

Conclusions

EUGR is not rare in preterm infants, especially those with small GA during the early stages of life, which is difficult to be improved within a short period of time. After discharge, feeding with fortified breast milk or PDF is more suitable to prevent EUGR in preterm infants than feeding with the pure breast milk or term formula milk.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Changhua Zhang and Liang Li) for the series "Nutritional Support for Digestive Surgery" published in *Digestive Medicine Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr.2019.03.04). The series "Nutritional Support for Digestive Surgery" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. As this was a retrospective study, informed consent was exempt.

References

1. Editorial Board of Chinese Journal of Pediatrics; Subspecialty Groups of Neonatology and Child Health Care, The Society of Pediatrics, Chinese Medical Association. Feeding recommendations for preterm infants and low birth weight infants. Zhonghua Er Ke Za Zhi 2009;47:508-10.
2. Pediatric Collaboratory Group, Parenteral and Enteral Nutrition Society, Chinese Medical Association; the Subspecialty Group of Neonatology, Pediatrics Society, Chinese Medical Association; the Subspecialty Group of Neonatology, Pediatric Surgical Society, Chinese Medical Association. Guide for clinical application of nutrition support in critical neonates in China. J Clin Pediatr 2013;31:1177-82.
3. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
4. Li H; Capital Institute of Pediatrics, Coordinating Study Group of Nine Cities on the Physical Growth and Development of Children. Growth standardized values and curves based on weight, length/height and head circumference for Chinese children under 7 years of age. Zhonghua Er Ke Za Zhi 2009;47:173-8.
5. Isaacs EB, Morley R, Lucas A. Early diet and general cognitive outcome at adolescence in children born at or below 30 weeks gestation. J Pediatr 2009;155:229-34.
6. Biasini A, Monti F, Laguardia MC, et al. High protein intake in human/maternal milk fortification for ≤1250 gr infants: intrahospital growth and neurodevelopmental outcome at two years. Acta Biomed 2018;88:470-6.
7. Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009;124:649-57.

8. Riskin A, Hartman C, Shamir R. Parenteral Nutrition in Very Low Birth Weight Preterm Infants. Isr Med Assoc J 2015;17:310-5.
9. Embleton ND, Simmer K. Practice of parenteral nutrition in VLBW and ELBW infants. World Rev Nutr Diet 2014;110:177-89.
10. Boo NY, Soon CC, Lye MS. Risk factors associated with feed intolerance in very low birthweight infants following initiation of enteral feeds during the first 72 hours of life. J Trop Pediatr 2000;46:272-7.
11. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics 2003;111:986-90.
12. Research Group for the Nutrition of Premature Infants, Wang DH. Multicenter study of the nutritional status of premature infants in neonatal intensive care unit in China: report of 974 cases. Zhonghua Er Ke Za Zhi 2009;47:12-7.
13. Tozzi MG, Moscuzza F, Michelucci A, et al. ExtraUterine Growth Restriction (EUGR) in Preterm Infants: Growth Patterns, Nutrition, and Epigenetic Markers. A Pilot Study. Front Pediatr 2018;6:408.
14. Gonzalez-Rodriguez P, Cantu J, O'Neil D, et al. Alterations in expression of imprinted genes from the H19/IGF2 loci in a multigenerational model of intrauterine growth restriction (IUGR). Am J Obstet Gynecol 2016;214:625.e1-625.e11.
15. Bloom BT, Mulligan J, Arnold C, et al. Improving growth of very low birth weight infants in the first 28 days. Pediatrics 2003;112:8-14.
16. Krcho P, Vojtova V, Benesova M. Analysis of Human Milk Composition After Preterm Delivery With and Without Fortification. Matern Child Health J 2015;19:1657-61.
17. Maas C, Mathes M, Bleeker C, et al. Effect of Increased Enteral Protein Intake on Growth in Human Milk-Fed Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr 2017;171:16-22.

doi: 10.21037/dmr.2019.03.04
Cite this article as: Li G, Zhang A, Lin H, Wang M, Fang X, Yang S, Lin N. Analysis of nutritional status of preterm infants at early life. Dig Med Res 2019;2:5.

