

Early administration of amino acids with different doses in low birth weight premature infants

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Background: The reasonable use of amino acids (AAs) in parenteral nutrition (PN) is very critical to the growth and development of premature infants. However, the appropriate dose of AAs has not been determined. Our study was designed to investigate the clinical effect of two different doses of AAs in PN for low birth weight premature infants. **Materials and Methods:** This randomized controlled study included 191 preterm infants who admitted to the neonatal intensive care unit of the First Affiliated Hospital of Nanjing Medical University from June 2015 to December 2016 and they were randomly divided into Group 1 ($n = 81$) and Group 2 ($n = 110$). In Group 1, the starting dose of AAs dose was 1.0–1.5 g/kg/day, which was increased by 0.5 g/kg with the maximum dose at 3.5 g/kg/day. In Group 2, the starting dose of AAs was 1.8–2.5 g/kg/day and was increased by 1.0 g/kg with the maximum dose at 4.0–4.5 g/kg/day. We analyzed the clinical characteristics, body weight, body length, total calorie intake, nonprotein calorie intake, total protein intake, liver and kidney function, and complications of the two groups of preterm infants. **Results:** The start of enteral feeding and the recovery of birth weight in Group 2 were earlier than those in Group 1 (3.83 ± 3.15 day vs. 5.53 ± 5.63 day, $P = 0.016$ and 6.36 ± 4.88 day vs. 8.48 ± 9.27 day, $P = 0.043$, respectively). The duration of PN and the time before total enteral nutrition were shorter in Group 2 than in Group 1 (16.46 ± 10.33 day vs. 21.41 ± 18.00 day, $P = 0.029$ and 15.47 ± 10.54 day vs. 19.47 ± 14.57 day, $P = 0.038$; respectively). The duration of mechanical ventilation (1.12 ± 2.62 day vs. 3.31 ± 8.13 day, $P = 0.028$) in Group 2 was shorter than that in Group 1. **Conclusion:** High doses of AAs in the early PN for preterm infants facilitate the promotion of early growth and development, advance recovery of birth weight, reduce the duration of PN, and reduce respiratory support without increasing the incidence of complications.

Key words: Amino acids, growth and development, parenteral nutrition, preterm infants

How to cite this article: Li Y, Sun Z, Hu Y, Li B, Bu X, Luo Y, *et al.* Early administration of amino acids with different doses in low birth weight premature infants. *J Res Med Sci* 2020;25:49.

INTRODUCTION

In comparison to term infants, preterm infants have less lean body mass and require a higher amount of protein and amino acids (AAs).^[1] Owing to their immature digestive system and little nutrient storage, enteral nutrition often fails to fulfill the metabolic requirements of low birth weight (LBW) premature infants.^[2] In such infants, the initiation of parenteral nutrition (PN) is recommended within 24 h after birth to maintain positive nitrogen balance and ensure extrauterine growth and development.^[3] The insufficient supply of AAs, one of the three nutrients in PN, cannot compensate for nitrogen depletion, which

can result in the catabolic state. However, high doses of AAs also tend to amplify the metabolic burden of premature infants. At present, PN support programs still use the initial dose of AA 1.0–1.5 g/kg/day and increase the daily dose by 0.5 g/kg to the maximum dose of 3.5 g/kg/day commonly.^[4] In recent years, the American Academy of Pediatrics has recommended that preterm infants be given AA 3.0 g/kg/day immediately after birth, gradually increasing to 4.0 g/kg/day.^[5] The European Society for Pediatric Gastroenterology and Hepatology and Nutrition Committee on Nutrition recommended an intake of AAs of 3–4.5 g/kg/day for enteral nutrition in premature infants.^[6] Hence, the initial dose, increasing dose, and maximum dose of AA

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DOI:

10.4103/jrms.JRMS_213_19

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Submitted: 03-May-2019; **Revised:** 22-Oct-2019; **Accepted:** 15-Mar-2020; **Published:** 22-May-2020

in PN are still controversial. To examine the adequate dose of AAs in PN of the LBW premature infants and evaluate its efficacy and safety, we prospectively assigned two different doses of AA nutrition to 191 LBW preterm infants and assessed the growth and metabolism of preterm infants in both strategies.

MATERIALS AND METHODS

Study subjects

This was a randomized controlled study comprising 200 preterm infants admitted to the neonatal intensive care unit (NICU) of the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) between June 2015 and December 2016. The inclusion criteria were as follows: gestational age, <37 weeks; birth weight, <2500 g; and being admitted to NICU within 1 h after birth. The exclusion criteria were severe congenital malformation, congenital heart diseases, abandoning treatment or death, or no informed consent provided by parents. The consort diagram of studied population is shown in Figure 1. These preterm infants were randomly divided into Group 1 ($n = 99$) and Group 2 ($n = 101$) using random number generation. In Group 1, there were four cases of premature infants with incomplete information, while in Group 2, there was one case. There were three cases in Group 1 and one case in Group 2 with incomplete treatment, respectively. The

parents of 11 twins in Group 1 insisted that the twins must receive the same treatment, requested to enter Group 2. Finally, there are 81 preterm infants in Group 1 and 110 preterm infants in Group 2. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (ethical approval number: 2015-SR-031).

Nutrient administration

In all enrolled infants, PN was initiated within 2 h after birth. PN comprised glucose, AAs, lipid emulsion, water, electrolytes, vitamins, and trace elements and was formulated according to the Chinese guidelines for the use of nutritional support in critically ill neonates in 2013.^[3] Furthermore, intravenous lipid emulsion was lipofundin medium chain triglycerides / long chain triglycerides (MCT/LCT)", which was produced by B. Braun Melsungen AG. All patients were administered water-soluble vitamins and lipid-soluble vitamins produced by Fresenius Kabi.

Based on the attending medical officer's selection of AA solutions, premature infants were divided into two groups. For AAs, we selected compound AA injection (I9aa-i; 6%; BJ Double-Crane). In Group 1, the starting dose of AAs dose was 1.0–1.5 g/kg/day, which was increased by 0.5 g/kg with the maximum dose at 3.5 g/kg/day. In Group 2, the starting dose of AAs was 1.8–2.5 g/kg/day which was increased by 1.0 g/kg with the maximum dose at 4.0–4.5 g/kg/day.^[4-6] To

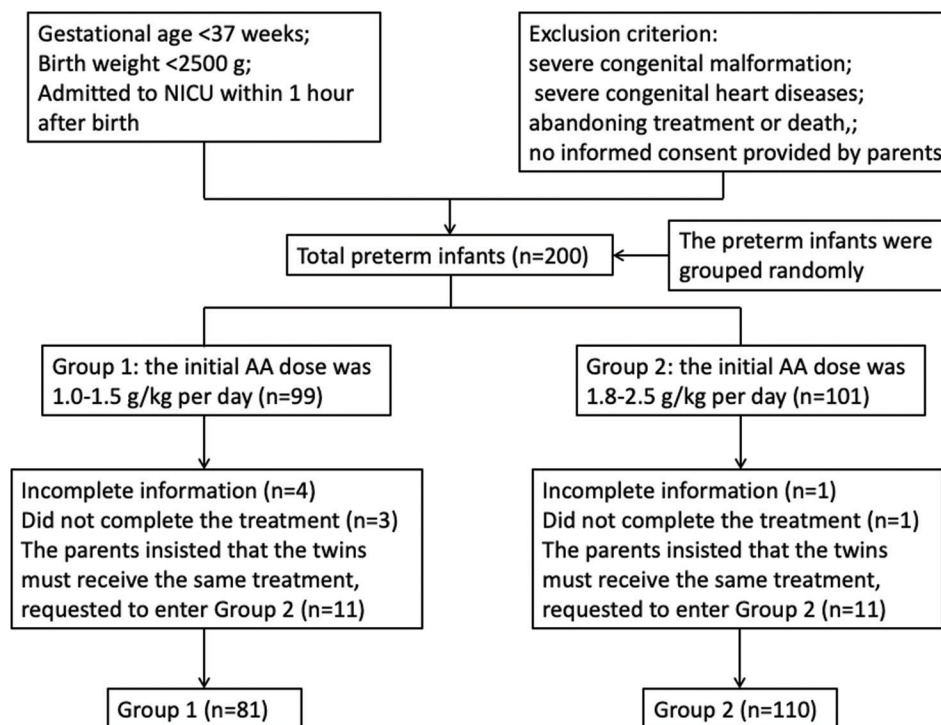


Figure 1: A total of 200 prematures admitted to the neonatal intensive care unit from June 2015 to December 2016 were randomly divided into two groups. In Group 1 ($n = 99$), the starting dose of amino acids dose was 1.0–1.5 g/kg/day. In Group 2 ($n = 101$), the starting dose of amino acids was 1.8–2.5 g/kg/day. However, in two groups, there were 4 versus 1 prematures with incomplete information and 3 versus 1 prematures with incomplete treatment. The parents of 11 twins in Group 1 insisted that the twins must receive the same treatment, requested to enter Group 2. Finally, there are 81 prematures in Group 1 and 110 prematures in Group 2

eliminate the possibility of any bias, study participants, clinicians, and observers were blinded to the research by following the blinding method. The main clinical indexes included: (a) sex, gestational age, birth weight, birth length, initiation of enteral feeding, time before total enteral nutrition, and maximum loss of body weight; (b) height and weight; (c) laboratory values during the initial 14 days of life, such as serum pH, bicarbonate, serum urea nitrogen, and serum creatinine; and (d) complications in study infants such as necrotizing enterocolitis (NEC), septicemia, and cholestasis.

Statistical analysis

In this study, EpiData 3.1 software (The EpiData Association, Denmark) was used for data recording, and SPSS 11.0 (IBM SPSS Statistics, United States) software was used for statistical analysis. The categorical data are presented as actual numbers or percentages (%), and the groups were compared by the Chi-square test or Fisher's exact test. The normally distributed data are presented as mean \pm standard deviation and groups were compared by the *t*-test, while nonnormally distributed data were compared using the Wilcoxon test. Furthermore, the correlative factor analysis of cholestasis and extrauterine growth retardation (EUGR) was performed using the logistic regression analysis. In addition, $P < 0.05$ was considered a statistically significant value.

RESULTS

In this study, 81 and 110 premature neonates were placed in Groups 1 and 2, respectively. Of all, 51.3% were male and 48.7% were female. No significant differences were observed between two groups in the baseline data of sex composition, gestational age, birth weight, birth length, and the incidence of neonatal asphyxia and small for gestational age [$P > 0.05$; Table 1]. The

initiation of enteral feeding (5.53 ± 5.63 day vs. 3.83 ± 3.15 day; $P = 0.016$), the total enteral nutrition (19.47 ± 14.57 day vs. 15.47 ± 10.54 day; $P = 0.038$), and the recovery of birth weight (8.48 ± 9.27 day vs. 6.36 ± 4.88 day; $P = 0.043$) in Group 2 were earlier than those in Group 1. The duration of PN (21.41 ± 18.00 day vs. 16.46 ± 10.33 day; $P = 0.029$), mechanical ventilation (3.31 ± 8.13 day vs. 1.12 ± 2.62 day; $P = 0.028$), hospitalization duration (23.33 ± 14.57 day vs. 20.13 ± 11.66 day; $P = 0.105$), and duration of oxygen therapy (4.69 ± 8.36 day vs. 2.88 ± 5.55 day; $P = 0.115$) were shorter and the hospitalization expenses ($36,421.74 \pm 70,983.72$ Yuan vs. $24,769.95 \pm 16,072.59$ Yuan; $P = 0.151$) were lower in Group 2 than those in Group 1. Table 1 summarizes the details of patients' characteristics and data. Furthermore, no significant differences were observed in laboratory findings on the 1st, 7th, and 14th day during hospitalization between both groups [$P > 0.05$; Table 2].

Within 2 weeks after birth, the length and weight of premature infants in Group 2 were greater than those in Group 1 within 2 weeks after birth; however, they did not vary significantly between two groups [$P > 0.05$; Figure 2a and b].

Within 2 weeks after birth, while the total calorie intake and nonprotein calorie intake of preterm infants in Group 2 were higher than those in Group 1, the overall statistical significance was not evident [$P > 0.05$; Figure 2c-f]. On the 1st and 2nd day after admission, the total protein ingestion and the proportion of protein calorie in Group 2 were higher than that in Group 1 ($P < 0.05$). Although differences were noted between both groups a few days later, they were not statistically significant ($P > 0.05$).

Table 3 illustrates the incidences of complications in both groups. Apparently, the incidence of respiratory distress

Table 1: Clinical characteristics of study infants

	Group 1 (n=81)	Group 2 (n=110)	P
Sex (male:female)	41:40	57:53	0.870
Gestational age (week)	32.71 \pm 2.30	33.31 \pm 1.97	0.061
Born by cesarean	59 (72.8)	83 (75.5)	0.683
Birth weight (g)	1796.42 \pm 401.61	1853.36 \pm 378.88	0.318
Birth length (cm)	42.65 \pm 3.10	42.83 \pm 2.88	0.680
SGA	21 (25.9)	35 (31.8)	0.355
Neonatal asphyxia	18 (22.2)	25 (22.7)	0.934
Start of enteral feeding (days)	5.53 \pm 5.63	3.83 \pm 3.15	0.016
Start of total enteral nutrition (days)	19.47 \pm 14.57	15.47 \pm 10.54	0.038
Duration of parenteral nutrition (days)	21.41 \pm 18.00	16.46 \pm 10.33	0.029
Maximum loss of body weight (g)	86.06 \pm 98.52	66.16 \pm 67.21	0.099
Recovery of birth weight (days)	8.48 \pm 9.27	6.36 \pm 4.88	0.043
Duration of hospital stay (days)	23.33 \pm 14.57	20.13 \pm 11.66	0.105
Hospitalization expenses (Yuan)	36421.74 \pm 70,983.72	24,769.95 \pm 16,072.59	0.151
Duration of mechanical ventilation (days)	3.31 \pm 8.13	1.12 \pm 2.62	0.028
Time of oxygen therapy	4.69 \pm 8.36	2.88 \pm 5.55	0.115

SGA=Small for gestational age

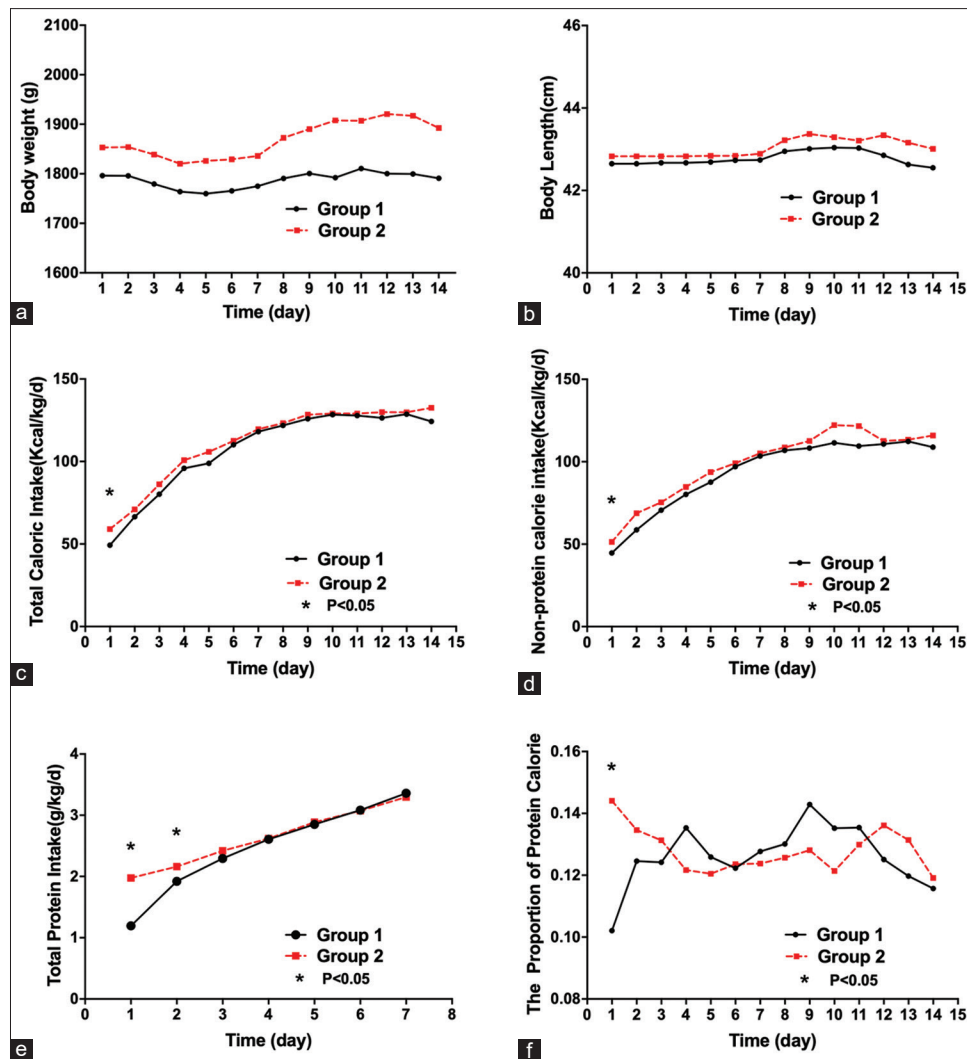


Figure 2: (a) The body weight of premature infants in two groups within 2 weeks after birth. (b) The body length of premature infants in two groups within 2 weeks after birth. (c) The total calorie intake of premature infants in two groups within 2 weeks after birth. (d) Nonprotein calorie intake of premature infants in two groups within 2 weeks after birth. (e) The total protein intake of premature infants in two groups within 1 week after birth. (f) The proportion of protein calorie of premature infants in two groups within 2 weeks after birth. * $P < 0.05$

syndrome (RDS) in both groups was 35.8% and 20.91%, respectively, implying a statistically significant difference between them ($P = 0.022$). Notably, the rate of hypokalemia in Group 2 was higher than that in Group 1. In addition, no significant differences were noted in the incidence of other complications between the two groups.

We analyzed the logistic regression. EUGR was dependent variables, and the characteristics of the study infants with different values between Group 1 and 2 in Table 1 were included as independent variables. The time before total enteral nutrition was a risk factor for EUGR [$P < 0.05$; Table 4].

DISCUSSION

Owing to poor nutrient deposition, incoordination of sucking and swallowing, and limited viability, premature infants often exhibit growth retardation after birth. A large

part of the reason for the premature infant's EUGR is due to the insufficient supply of energy and protein, resulting in the negative nitrogen balance of the infant, unable to meet the needs of its own metabolism and growth.^[7] Complications such as intraventricular hemorrhage, bronchopulmonary dysplasia (BPD), and their involvements in this process may result in longer period of hospitalization for the newborn and in the long run make the living conditions more difficult.^[8,9] The gastrointestinal function of premature infants has not yet matured, and enteral nutrition provides limited energy. Therefore, PN should be used as early as possible within 24 h after birth.^[3]

The reasonable use of AAs in the PN is very critical to the growth and development of premature infants. The early application of AAs after birth can avoid early malnutrition, prevent the occurrence of extrauterine developmental retardation, and promote the development

Table 2: Laboratory values during the initial 14 days of life

	Group 1 (n=81)	Group 2 (n=110)	P
Day 1			
Serum pH	7.25±0.07	7.27±0.07	0.067
Bicarbonate (mmol/l)	21.66±2.69	21.27±2.90	0.358
Total bilirubin (µmol/l)	41.22±26.22	40.81±23.40	0.910
Direct bilirubin (µmol/l)	12.06±3.15	12.79±2.77	0.092
Serum ALT (U/L)	7.27±8.88	6.66±3.29	0.505
Serum AST (U/L)	43.20±33.74	41.25±16.27	0.600
γ-glutamyl transpeptidase (U/L)	232.49±155.94	256.73±159.73	0.302
Serum urea nitrogen (mg/dl)	4.25±3.24	4.25±2.08	0.992
Serum creatinine (mg/dl)	71.58±58.06	62.26±22.14	0.129
Day 7			
Serum pH	7.39±0.06	7.39±0.06	0.944
Bicarbonate (mmol/L)	23.23±4.73	23.52±4.98	0.800
Total bilirubin (µmol/L)	134.65±41.50	134.38±42.08	0.981
Direct bilirubin (µmol/L)	16.60±16.22	14.92±4.01	0.607
Serum ALT (U/L)	9.30±14.07	8.03±4.62	0.644
Serum AST (U/L)	32.23±10.82	29.20±13.23	0.325
γ-glutamyl transpeptidase (U/L)	145.30±90.48	147.29±82.47	0.929
Serum urea nitrogen (mg/dl)	4.25±2.67	3.80±2.02	0.488
Serum creatinine (mg/dl)	63.38±23.32	55.24±17.83	0.148
Day 14			
Serum pH	7.41±0.07	7.40±0.04	0.587
Bicarbonate (mmol/l)	23.85±3.67	21.86±2.88	0.134
Total bilirubin (µmol/l)	90.70±35.71	96.95±43.30	0.762
Direct bilirubin (µmol/l)	18.55±17.42	15.15±3.08	0.571
Serum ALT (U/L)	6.54±5.28	7.25±2.37	0.737
Serum AST (U/L)	22.44±4.30	29.98±30.14	0.525
γ-glutamyl transpeptidase (U/L)	99.85±61.33	286.37±227.14	0.056
Serum urea nitrogen (mg/dl)	2.68±0.81	3.80±2.02	0.477
Serum creatinine (mg/dl)	47.40±9.91	54.08±19.74	0.433

ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

of nervous system.^[10] In 2004, the American Academy of Pediatrics Quality Improvement and Management Steering Committee recommended that early initial dose AA (2–3 g/kg/day) was more beneficial to the growth and development of premature infants than the previous 1.0–1.5 g/kg/day.^[11] In recent years, for using appropriate doses of early AAs, the American Academy of Pediatrics and the European Society for Pediatric Gastroenterology and Hepatology and Nutrition Committee on Nutrition have different recommendations.^[5,6] Till date, the initial dose, increasing dose, and maximum dose of AA in PN are still controversial. Therefore, to elucidate the impact of AAs in two different doses in PN on the growth and prognoses in LBW infants, this study assessed and compared AAs' dosages and clinical characteristics of 191 preterm infants, whose birth weight ranged from 1000 to 2500 g, providing

Table 3: Complications of study infants

	Group 1 (n=81)	Group 2 (n=110)	P
NEC	5 (6.17)	7 (6.36)	0.957
Septicemia	3 (37.0)	6 (5.45)	0.736
EUGR	16 (19.75)	14 (12.73)	0.187
Cholestasis	5 (6.17)	3 (2.73)	0.287
PDA	17 (20.99)	29 (26.36)	0.390
RDS	29 (35.80)	23 (20.91)	0.022
Hospital infection	0 (0)	1 (0.91)	0.999
Metabolic acidosis	35 (43.21)	39 (35.45)	0.277
Hyperglycemia	4 (4.94)	1 (0.91)	0.165
Leukopenia	30 (37.04)	49 (44.55)	0.298
Hypocalcemia	62 (76.54)	81 (73.64)	0.647
Hyponatremia	13 (16.05)	21 (19.09)	0.587
Kaliopenia	14 (17.28)	34 (30.91)	0.032
Hypomagnesemia	31 (38.27)	45 (40.91)	0.713

RDS=Respiratory distress syndrome; PDA=Patent ductus arteriosus; EUGR=Extrauterine growth retardation; NEC=Necrotizing enterocolitis

a reference to develop a reasonable AAs strategy in the future.

As per the guidelines of the American Academy of Pediatrics, the growth rate of preterm infants should duplicate the growth rate of age-matched fetuses and obtain a similar body composition. Thus, the protein intake of preterm infants should be analogous to that of age-matched fetuses in the uterus.^[12] Liu *et al.* stated that in comparison to the conventional strategy of PN, high doses of AA supplementation could significantly improve the growth and development of preterm infants after birth, shorten hospitalization period, and reduce hospitalization expenses.^[13]

In our study, the mean height and weight in Group 2 were better than those in Group 1, although the differences in both groups did not vary significantly. Group 2 had less time to recover birth weight than Group 1, and the difference was statistically significant. Within 2 weeks after birth, the total calorie intake, nonprotein calorie intake, and total protein intake in Group 2 were more than those in Group 1; however, the difference lacked statistical significance. However, the total protein intake of Group 2 preterm infants on the 1st and 2nd day after birth was higher than that of Group 1, and the proportion of protein calorie intake of Group 2 preterm infants on the 1st day after birth was higher than that of Group 1, showing statistically significant differences. This suggests that high dose of early AAs can meet the needs of premature infants for protein, shorten the time of body mass recovery, avoid the occurrence of early malnutrition in premature infants, and benefit the growth and development of premature infants, which is consistent with the research results of De Curtis and Rigo.^[14]

Ibrahim *et al.*^[15] took the AA of 2.7 g/kg/day as the starting dose of PN, which significantly improved the nutritional

Table 4: Logistic regression analysis of extrauterine growth retardation

	β coefficient	OR	95% CI	P
High-dose AAs (no=0, yes=1) ^a	-0.063	0.939	0.364-2.418	0.896
Start of enteral feeding (days)	0.039	1.040	0.931-1.160	0.489
Start of total enteral nutrition (days)	0.107	1.113	1.008-1.229	0.033
Duration of parenteral nutrition (days)	-0.048	0.953	0.856-1.061	0.379
Duration of mechanical ventilation (days)	0.049	0.999	0.995-1.004	0.678
Recovery of birth weight (days)	-0.010	0.990	0.905-1.082	0.823

^a“High doses of AAs” is “NO,” i.e., Group 1, the value is “0,” and was defined as reference category. AAs=Amino acids; OR=Odds ratio; CI=Confidence interval

status of premature infants, shortened the PN duration, and promoted the AAs of premature infants to reach the reference level of healthy fetuses. Our study suggested that compared with Group 1, the start of enteral feeding, the start of total enteral nutrition, and the recovery of birth weight in Group 2 were 1.7, 4.0, and 2.1 days earlier, respectively, and the PN duration was 4.9 days shorter, with statistically significant differences. This indicates that the AA dose of Group 2 can better promote the growth and development of premature infants.

Apparently, preterm infants have limited ability to synthesize some AAs. More essential AAs, such as cysteine, glutamine, histidine, taurine and tyrosine, were added to PN according to the composition and content of AAs in fetal and newborn blood to make PN solution safer. Furthermore, the addition of glutamine to PN can facilitate early improvement in liver function.^[16] The application of AAs in the early PN of preterm infants remains cautious due to the concern that excessive intake of AAs may lead to metabolic acidosis, hyperammonemia, renal insufficiency, and other complications. Since no significant differences were noted in alanine aminotransferase, aspartate aminotransferase, and γ -glutamyl transpeptidase between two groups, it indicates that high doses of AAs nutrition do not increase the burden of hepatic metabolism. The breakdown of protein results in urea nitrogen. Vlaardingerbroek *et al.*^[17] suggested that higher AA oxidation results in higher urea concentrations. However, our study reported no significant differences between two groups in urea nitrogen and creatinine values on the 1st, 7th, and 14th day during hospitalization, suggesting that high doses of AAs do not increase the kidney load.

Reportedly, high doses of AAs in PN could not only ensure the growth of preterm infants but also improve their breathing and reduce the incidence of bronchopulmonary dysplasia. While glucose in only PN can provide energy

or convert into fat, AAs can promote protein synthesis, increase pulmonary surfactant secretion, and sustain the lung development. Our study identified that the incidence of RDS in Group 2 was lower than that in Group 1 (20.91% vs. 35.80%), which was consistent with previous studies.^[18-20] In Group 2, the mean time of mechanical ventilation and oxygen therapy was shortened by 2.2 and 1.8 days, respectively. Therefore, early, full AA nutrition is effective in preterm infants' lung development and reducing pulmonary complications. Besides, PN-associated cholestasis (PNAC) is one of the common complications of PN in premature infants.^[21] The incidence of cholestasis in preterm infants with PN for more than 14 days was 28.2%.^[22] The long-term PN inhibits the secretion of gastrointestinal hormones in infants and disrupts emptying of the gallbladder.^[23] The results of our study found that the incidence of cholestasis in Group 2 was lower than that in Group 1 (2.73% vs. 6.17%), which was associated with advanced enteral feeding and short duration of PN. Rangel *et al.*^[24] had shown that the development of PNAC was related to the cumulative dosage of amino acid, not to its initial concentration and rate of increase. This also confirmed the safety of high-dose AAs in Group 2.

The incidence of hypokalemia in Group 2 was higher than that in Group 1 (17.28% vs. 30.91%), which might be related to the high level of osmotic pressure of PN in Group 2. There were no significant differences in other complications, such as sepsis, NEC, and patent ductus arteriosus, between two groups, proving the safety of high AAs doses strategies in the preterm infants' PN in our study.

In China, the Collaborative Group for the Nutritional, Growth, and Developmental Study on Very LBW Infants (VLBWIs) reported that the rate of EUGR in VLBWIs at discharge was 72.1%, which was 37.7% higher than the incidence rate of intrauterine growth retardation (IUGR). Furthermore, up to 59.2% infants with IUGR developed EUGR.^[25] In the past, the conservative AA dose in PN often led to the occurrence of EUGR. The incidence of EUGR in Group 2 was lower than that in Group 1 (12.73% vs. 19.75%), but the difference was not statistically significant. Logistic regression analysis suggested that the time before total enteral nutrition was a risk factor for EUGR. This suggests that we need to shorten the duration of PN as much as possible, which is consistent with the results of our study.

CONCLUSION

This study suggests that high doses of AAs in the early PN facilitate the promotion of early growth and development, advance recovery of birth weight, reduce the duration of PN, and reduce respiratory support. The data of preterm infants reported in this study are still in the follow-up

with no reported case of death or giving up the treatment. The laboratory findings of eight premature infants who were diagnosed with cholestasis in hospital reported their recovery. Further research is warranted on the growth and metabolic indexes of infants discharged from the hospital. However, by considering both groups not in the ratio of 1:1 and not comparing their long-term prognoses, we anticipate further studies that provide a more reasonable strategy of PN.

Acknowledgments

We sincerely appreciate the patients' parents for their understanding and support of our study. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanjing Medical University (NO. 2015-SR-031).

Financial support and sponsorship

This study supported by the National Natural Science Foundation of China (81300521) and Six Talent Peaks Project in Jiangsu Province (2016-WSN-090).

Conflicts of interest

There are no conflicts of interest.

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