Original Article

Amino acid dosing in parenteral nutrition for very low birth weight preterm neonates: an outcome assessment

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This study aimed to investigate the effects of parenteral nutrition (PN) administration of amino acids (AA) on physical changes among very low birth weight infants in a local hospital setting in Malaysia. A retrospective study was carried out at a hospital in Malaysia. Records of neonates prescribed PN in the neonatal unit in 2012 were screened for eligibility. A total of 199 premature neonates received PN support in the year 2012 and, of these, 100 fulfilled the inclusion criteria. The median value of AA intake on the first day of PN was 2.00 (<28 weeks group); 1.00 (28-31 weeks group) and 0.75 (>31 weeks group). Neonates in the <28 weeks group were more likely to receive AA at an earlier time and higher initial dose compared with the other age groups. The study also found that there was no statistically significant difference in the dose of AA on the first day of PN administration and that the significant variations in nutritional parameters among the subjects did not lead to differences in physical outcomes. This study identified that when PN is provided in the local hospital setting, it is likely that the current nutritional practices are inadequate to achieve the standard growth recommendations. Our findings call for a need to optimize AA and calorie intake since growth restriction is a morbidity which will affect the infants' growth and development. Current prescriptions for PN in this hospital need to be reviewed in order to improve patient outcomes.

Key Words: birth weight, nutritional requirements, growth and development, nutritional support, nutritional therapy

INTRODUCTION

Preterm birth is associated with major morbidities, particularly in respect of very low birth weight (VLBW) infants.[1] One of the major morbidities is abnormal neuro developmental outcomes, and this has been linked to inadequate nutrition during the early postnatal period.[2] Studies have demonstrated that these neonates often develop severe nutritional deficits during the first week after birth and inhibited growth during early life. Inadequate nutrition has been associated with poor long-term outcomes such as increased risk of infections, the need for mechanical ventilation and development of chronic lung diseases.[3]

Preterm infants are born with very little nutrient storage. Ho et al stated that 1% of an infant's protein stores will be lost daily if only intravenous dextrose is given to preterm infants.[4] In addition, the energy obtained from administering intravenous dextrose does not assist in producing more muscles or bones; rather that energy is converted into body fat.[5] Infants, in particular VLBW infants, have less well-developed lean body mass, and thus they require higher amounts of amino acids (AA) and protein to support the growth of lean body mass and tissue.[5]

According to the guidelines issued by the American Academy of Pediatrics, the postnatal growth rate of preterm infants should duplicate the foetal growth rate and mimic the body composition of the age-matched foetus. This is particularly crucial for their postnatal development and therefore their nutritional intake should imitate a similar gestational stage which the foetus would be exposed to if it were still in the uterus.[6,7] The goal of AA delivery to preterm infants is to produce an intravenous substrate that will allow protein deposition and subsequent gains in lean body mass that is comparable to that of the foetus

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in-utero.[8]

A recent systematic review suggests that the amount of AA required by preterm infants can be categorised as low AA intake (<2 g/kg/day), high AA intake (2-3 g/kg/day) and very high AA intake (>3 g/kg/day).[9] Although Koletzko et al demonstrated that a supplementation of 0.85-1.2 g/kg per day of AA did not result in a positive nitrogen balance,[10] Thureen et al reported that a mean intake of 0.9 g/kg per day of AA was sufficient to prevent significant protein loss.[11] Since an age-matched foetus will accrete protein at a rate of 1.5 g/kg per day, preterm infants should receive a similar level of protein supplementation.[12] This was also been discussed by Rivera et al who recommended that an intake of 1.5 g/kg per day of AA is necessary to prevent a negative nitrogen balance.[13] In another study by van Toledo-Eppinga et al, a minimal catabolic state was achieved for preterm infants when they received 1.8 g/kg per day of AA.[14] A positive nitrogen balance was also achieved with an intake of AA between 2.30-2.65 g/kg per day.[10]

In many institutions, it is a common practice to initiate AA infusion between zero and 36 hours of life.[4,12] However, there are no standard guidelines as to how to initiate the AA dose in preterm infants. Most often, AA administration begins at 0.5 or 1.0 g/kg per day and is incremented to 3.0 g/kg per day over several days.[12] Following Australasian Neonatal Parenteral Nutrition Consensus Group recommendations, from July 2011, preterm infants born at less than 32 weeks in New South Wales, Australia, are given a regimen of three standard and two optional amino acid/dextrose formulations and one lipid emulsion. This is a total transformation of previous practice, which involved 61 different neonatal standardised parenteral nutrition (PN) formulations with different AA, dextrose and lipid compositions.[15,16] The new consensus aims at higher AA intakes of 4 g/kg using 33 g/L and 30 g/L PN solution compared with the previous practice of 3 g/kg using 20 g/L PN solution.[16] In Malaysia, however, current PN practices are heavily dependent on the use of commercialized pre-packed PN bags which could be three or two chamber bags (containing AA, glucose with or without lipid). This practice imposes significant restrictions on the ability to adjust the dosing of AA because the AA content in these pre-packed bags are identical and fixed. Thus, neonates often receive a lower than recommended level of AA, as has previously been observed by Thomas and Sinn.[17]

To the best of the author's knowledge, there were no similar studies available in the existing literature that have focused on PN administration among preterm infants in local settings.[18] Thus, this study focused on investigating how the PN administration of AA influences physical changes among VLBW infants in local hospital settings.

METHODS

Study design

A retrospective study was carried out at a main referral hospital in the state of Johor, Malaysia. VLBW neonates prescribed PN in the neonatal intensive care unit of this hospital between January 2012 and December 2012 was included in this study. A flow chart summarizing the screening process is given in Figure 1.

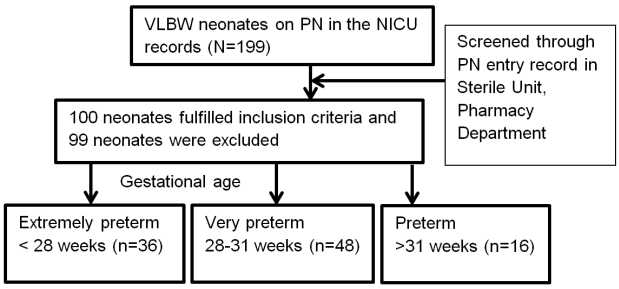

Figure 1. Flow chart of the study group

This study was registered with the Malaysian National Medical Research Registry and obtained ethical approval from the Medical Research Ethics Committee, Ministry of Health Malaysia (Approval number: 16567). Patients' confidentiality was strictly maintained.

Patient selection criteria

Preterm neonates are defined as infants who are born before 37 completed weeks of gestation.[2] Very low birth weight (VLBW) refers to those who weigh less than 1500 g.[5,19] They can be further classified based on their gestational age. The study subjects, therefore, comprised preterm infants with a gestational age of less than 37 weeks and a birth weight of less than 1500 g, who had been prescribed PN at the hospital. Preterm infants who died within five days of birth, or who received PN for less than five days, together with those who were born with a congenital disease or metabolic problems, and those whose records contained missing data, were excluded from the study.

Nutrient administration

All preterm infants received AA (Vaminolact® 6.53%, Fresenius Kabi) through PN. The dose was determined by the attending medical officer based on a rule of thumb, which ranged from 0.5-2.0 g/kg per day on the first day of PN. The maximum dose was 3.0-3.5 g/kg per day.

The final glucose concentration in the PN solution ranged from 5.0-15.0%. The dose depended on the preterm infants' calorie needs and was determined by the attending medical officer.

IV lipid emulsion was initiated as early as the first day of PN. The starting dose was 0.5 g/kg per day and was increased by 0.5 g/kg, with the recommended maximum dose being 3.0 g/kg per day (Lipofundin® MCT/LCT 20%, B.Braun).

The electrolyte dose was determined according to the individual requirements of the preterm neonates. The patients were given water-soluble vitamins (Soluvit N®, Fresenius Kabi), lipid-soluble vitamins (Vitalipid Infant®, Fresenius Kabi) and trace elements (Peditrace®, Fresenius Kabi) according to the standard dose (4 mL/kg and 1 mL/kg, respectively).

Measurement of outcomes

The outcomes measured were physical changes such as weight, length and head circumference. The changes in these parameters were measured in respect to the initial

values at the start and end of PN, and the values reported here, therefore, refer to the weight, head circumference or length gained during the whole course of the PN regimen. Gains in weight, head circumference or length are recorded as positive outcomes, whereas decreases in any of the three parameters were recorded as negative outcomes.

The percentage change in the parameters was determined by dividing the final parameters with the initial parameters and then multiplying by 100.

Data collection

Clinical data related to growth and nutrition was obtained and recorded directly from the PN monitoring notes and patient medical records. The subjects were classified into three groups based on gestational age, namely as extremely preterm (<28 weeks), very preterm (28-31 weeks) and preterm (>31 weeks).

The data collected from the notes were gestational age, the days of life when PN was initiated, the days of life when PN was terminated, duration of PN, PN regimens, weight, length and head circumference at birth, current weight, length and head circumference and total calories. The data were collected through retrospective chart review and recorded on a standardized data collection form. In all cases, the data from the medical records was accepted as accurate.

Statistical analyses and sample size calculation

A sample size was calculated using a formula devised by Krejcie and Morgan.[20] The number of premature neonates referred for PN support in year 2012 in this hospital was 199. Based on the formula used, a total of 131 subjects were required to represent a cross-section of the population. After the exclusion criteria were applied, 100 patients were included in the final data analysis.

The data was analysed using SPSS version 18.0. The numeric data was expressed as mean±SD for parametric data, and median (Interquartile range) for non-parametric data. The categorical data was expressed as a number (percentage). Descriptive analysis was performed for all potential covariates, outcome measures and results. One-way analysis of variance (ANOVA) was used to measure the difference in physical changes between the three groups of gestational age. The Kruskal-Wallis test was performed for non-parametric data.

RESULTS

A total of 199 premature neonates received PN support at this hospital during 2012 and 100 preterm neonates were finally included. Overall, 52.0% of the subjects were females and 48.0% males. The data showed that the majority of the subjects were classified as being of Malay ethnicity (59.0%), while the remaining subjects were of other ethnicities, such as Indian, Chinese and Aboriginal. The gestational age of the patients ranged from 24-35 weeks, with an average of 28.9±2.72 weeks. The average birth weight was 1053±242 g. The mean birth length and head circumference of the infants was found to be 36.4± 3.51 cm and 25.6±2.19 cm, respectively. The details of the demographic data and patient characteristics are summarized in Table 1.

Information on nutritional intake during the study period is shown in Table 2. It can be seen that the patients in the <28 weeks group were initiated with AA at an earlier time compared to the other groups (3.83 vs 4.06 and 5.75 days, respectively). Those in the <28 weeks also received a higher dose of AA on the first day of PN compared with the other groups. However, no statistically significant difference was observed in the dose of AA applied on the first day of PN administration among the patients.

Total energy intake on the first day of PN administration was found to be significantly higher in the >31 weeks group (p=0.002). Throughout the course of PN administration, it was found that the <28 weeks neonates received more calories either by PN alone or by combination nutrition with enteral feeding; even though total energy intake by PN and combined nutrition did not vary significantly among the groups**.** Similarly, age of initiating enteral nutrition (EN) and duration of PN did not vary significantly between the groups. Evaluation of the regimen revealed that majority of the infants did not achieve the minimum standard nutritional goal of 100 kcal/kg/day

Table 1. Demographic and patient characteristics

	Gestational age			All (n=100)
	<28 weeks (n=36)	28-31 weeks (n=48)	>31 weeks (n=16)	
Gender†				
Men	19 (52.8)	22 (45.8)	7 (43.8)	48 (48.0)
Women	17 (47.2)	26 (54.2)	9 (56.3)	52 (52.0)
Ethnicity†				
Malay	23 (63.9)	26 (54.2)	10 (62.5)	59 (59.0)
Others	13 (36.1)	22 (45.8)	6 (37.5)	41 (41.0)
Gestational age (weeks)‡	26.0±0.94 (24-27)	29.6±1.04 (28-31)	33.3±1.24 (32-35)	28.9±2.72 (24-35)
Birth weight (g)‡	864±167 (600-1210)	1138±206 (600-1500)	1220±225 (750-1500)	1053±242 (600-1500)
Length (cm)‡	33.9±2.55 (29-40)	37.6±3.25 (28-45)	38.3±2.98 (33-43)	36.4±3.51 (28-45)
Head circumference (cm)‡	23.7±1.80 (20.5-27.5)	26.4±1.55 (24.0-30.0)	27.4±1.62 (24.0-29.0)	25.6±2.19 (20.5-30.0)

†Expressed as N (%); ‡Expressed as mean±SD (range).

Table 2. Nutritional intake in the VLBW infants based on gestational age

	Gestational age			All (n=100)	F (df)	*p*-value
	<28 weeks (n=36)	28-31 weeks (n=48)	>31 weeks (n=16)			
Age at introduction of AA (days of age)[†]	3.83±2.37 (1-12)	4.06±2.51 (1-11)	5.75±2.59 (1-12)	4.25±2.54 (1-12)	3.58 (2;97)	0.03[a,c]
Age at EN (days of age)[‡]	8.00 (6.00) (4-25)	7.50 (4.00) (2-24)	8.00 (6.50) (3-32)	8.00 (5.00) (2-32)	2.67 (2)	0.26[b]
Duration of PN (days)[‡]	15.5 (12.5) (6-79)	12.5 (7.75) (6-62)	9.50 (11.50) (5-33)	13.0 (10.0) (5-79)	3.46 (2)	0.18[b]
AA intake on the first day of PN (g/kg/day)[‡]	2.00 (1.38) (0.5-2)	1.00 (1.50) (0.5-2)	0.75 (0.50) (0.5-2.5)	1.00 (1.50) (0.5-2.5)	6.34 (2)	0.04[b]
Total energy intake on the first day of PN (kcal/kg/day)[†]	53.6±12.2 (37.0-81.5)	55.0±13.0 (30.5-92.6)	66.5±10.9 (44.2-86.1)	56.3±13.1 (30.5-92. 6)	6.55 (2;97)	0.002[a,d]
Total energy intake by PN (kcal/kg/day)[†]	81.3±8.91 (62.9-98.9)	77.2±77.6 (58.3-92.9)	76.8±12.1 (58.6-104)	78.6±9.99 (58.3-104)	2.12 (2;97)	0.13[a]
Total energy intake by PN and EN (kcal/kg/day)[†]	93.1±9.80 (73.8-110)	91.2±10.5 (65.0-110)	92.8±13.7 (74.2-126)	92.2±10.7 (65.0-126)	0.34 (2;97)	0.71[a]

VLBW: very low birth weight; AA: amino acids; EN: enteral nutrition; PN: parenteral nutrition.
[†]Expressed as mean±SD (range).
[‡]Expressed as median (interquartile range) (range).
[a]One-way ANOVA.
[b]Kruskal-Wallis test.
[c]Only "<28 weeks and >31 weeks" pair was significantly different using post-hoc test Scheffe procedure.
[d]Only "<28 weeks and >31 weeks" and "28-31 weeks and >31 weeks" pairs were significantly different using post-hoc test Scheffe procedure.

by PN.[21,22] The majority required a combination of PN with EN to achieve the minimum nutritional goal, as presented in Figure 2 (33% versus 81%, respectively).

The primary outcomes of weight gain, and increases in length and head circumference are shown in Tables 3, 4 and 5, respectively. It can be seen that the overall mean percentage of weight gain per day, median percentage of length growth per week and median percentage of head circumference growth per week was 0.30±0.82%, 0.89 (2.25)% and 1.32(1.42)%, respectively. It was observed that the percentage of weight gain, length and head circumference growth achieved by the premature infants does not vary significantly between the three gestational age groups (p>0.05).

DISCUSSION

Amino acids are necessary for the growth and development of the foetus. Administering AA and PN is safe and offers numerous benefits in terms of growth and neurodevelopment of preterm neonates.[12,17]

In this study, it was observed that the overall mean percentage weight gain per day achieved by the sample was 0.30±0.82%. The results revealed that the >31 weeks age group achieved a higher percentage of weight gain, which is probably due to the concurrent EN supplementation. It is also worth noting that in the case of several infants in the <28 weeks subgroup PN was terminated even the infants had not regained the normal birth weight. This result conforms with that of a large study of VLBW preterm

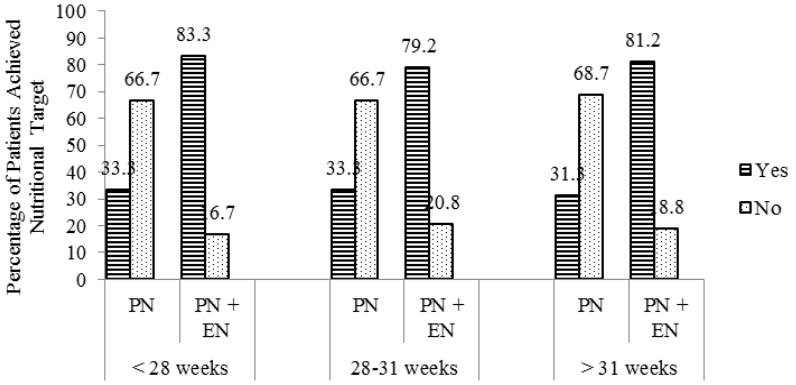

Figure 2. Regimen evaluation by PN and combined nutrition

Table 3. Weight gain outcome in the VLBW infants

	n	Weight at start of PN (g)	Weight at end of PN (g)	% of weight gain per day (g)	p-value
<28 weeks	36	827±170 (495-1235)	897±229 (510-1500)	0.17±0.78 (-1.80-2.04)	0.06†
28-31 weeks	48	1082±199 (600-1539)	1134±215 (625-1605)	0.25±0.86 (-2.56-2.73)	
>31 weeks	16	1215±203 (855-1500)	1324±208 (1000-1700)	0.73±0.68 (-0.22-2.08)	
All	100	1012±238 (495-1539)	1079±265 (510-1700)	0.30±0.82 (-2.56-2.73)	

VLBW: very low birth weight; PN: parenteral nutrition. All values were expressed as mean±SD (range).
†One-way ANOVA.

Table 4. Length growth outcome in the VLBW infants

	n	Length at start of PN (cm)	Length at end of PN (cm)	% of length growth per week (cm)	p-value
<28 weeks	36	33.9±2.55 (29-40)	35.0±3.40 (27-41)	0.91 (2.44) (-9.94-5.02)	0.39†
28-31 weeks	48	37.6±3.25 (28-45)	38.4±2.61 (30-44)	1.15 (2.56) (-9.72-9.21)	
>31 weeks	16	38.3±2.98 (33-43)	39.0±3.00 (33.5-43)	0.31 (1.30) (-3.68-4.33)	
All	100	36.4±3.51 (28-45)	37.3±3.40 (27-44)	0.89 (2.25) (-9.94-9.21)	

VLBW: very low birth weight; PN: parenteral nutrition. All values were expressed as mean±SD (range) except for % length growth per week expressed as median (IQR) (range).
†Kruskal-Wallis test.

Table 5. Head circumference growth outcome in the VLBW infants

	n	Head circumference at start of PN (cm)	Head circumference at end of PN (cm)	% of Head circumference growth per week (cm)	p-value
<28 weeks	36	23.7±1.80 (20.5-27.5)	24.1±2.24 (19-30)	1.62 (2.70) (-11.1-3.70)	0.83†
28-31 weeks	48	26.4±1.55 (24-30)	26.6±1.78 (23-31)	0.90 (1.21) (-12.7-14.0)	
>31 weeks	16	27.4±1.62 (24-29)	27.8±1.32 (25-29.5)	1.43 (1.67) (-5.00-4.61)	
All	100	25.6±2.19 (20.5-30)	25.9±2.35 (19-31)	1.32 (1.42) (-12.7-14.0)	

VLBW: very low birth weight; PN: parenteral nutrition. All values were expressed as mean±SD (range) except for % head circumference growth per week expressed as median (IQR) (range).
†Kruskal-Wallis test.

infants in Japan, which reported that up to 40% of the sample received PN, with these infants exhibiting significantly greater weight gain and head growth.[23] Nevertheless, the overall weight gain for the current study sample was lower than those reported in previous studies. Wright et al reported a weight gain of 18-20 g/day among the VLBW infants in their study.[24] Paul et al reported an increase in weight at a rate of 15.7±7.20 g/kg/day among extremely low birth weight infants.[25] Meanwhile, Guzmán et al reported an increase in weight of about 19 g/day at the end of PN in their study.[26] The goal for preterm infants is to gain weight at a rate of approximately 15 g/kg/day, which is the expected intrauterine rate of growth for a foetus.[27,28] The lower weight gain achieved for sample in this study may be due to the low level of AA and calories provided to the premature infants.

Even though there were differences between the groups in terms of the duration of PN, the days on AA and the total calories provided by PN or combined nutrition, the variation in percentage of weight changes per day was found to be statistically insignificant. These findings agreed well with other published studies.[24-26] Paul et al found that there was no significant difference in body weight after day ten between the five subgroups in their study.[25] Wright et al also found that there was no significant difference in the weight gain per day across four groups of VLBW infants.[24] A study by Guzmán et al found no difference in weight gain between their <1000 g group and their 1001-1250 g group.[26]

One possible explanation for the above findings is the weight velocity profile in premature infants was not linear as expected.[29] There are four phases in the weight gain of premature infants. The first phase is weight loss, the second phase is weight gain that is parallel to a foetal weight curve, the third phase is growth acceleration and the fourth phase is stability of growth along the individual centile.[30,31] It therefore seems prudent to suggest that majority of the neonate in this study were at first and fourth phases of the cycle.

The median percentage of length growth in this study was less compared with those reported by previous studies. Wright et al observed an increase in length between 0.8 and 1 cm per week in their study.[24] However, their results showed that there was no significant difference in the length increase between the four subgroups of their study, which is in agreement with the findings of this study. Hermann and Hermann reported that the length values declined below the 10th percentile for all gestational age groups in their study.[6] Although a detailed explanation was not provided for their observation, they obtained a mean length growth which was greater than the mean length growth observed in their reference study. It is recommended that the growth length should be similar as in the intrauterine rates, which is approximately one cm per week.[19]

The final physical outcome examined in this study is the increase in head circumference of the premature infants. The results revealed that the overall median percentage of head circumference increment per day in this study's sample was less than the recommended value for head circumference growth (0.5-0.8 cm per week), which is the growth rate similar to *in-utero* foetal growth.[6] The results also showed that there was no statistical difference in the median percentage of head circumference growth per kg per day between birth weight and gestational age subgroups. This is in line with Wright et al in which there was no statistical difference in the head circumference growth observed between four subgroups of VLBW that ranged from 0.71-0.74 cm per week.[24]

Weight, length and head circumference measurements are important markers for monitoring growth during infancy and childhood.[32] Poor nutritional status is usually associated with small values of weight and length, whereas head circumference measurements are related to the brain size during infancy.[32] Bloom et al carried out a quality improvement project that targeted weight gain in ELBW and VLBW infants during the first 28 days of life, with high weight gain being observed at sites where nutritional management practices were implemented.[33] They concluded that nutritional management practices led to significant improvements in weight and head circumference.

The fact that the increase in weight, length and head circumference observed in this study was less than the standard recommendations and those reported in other studies revealed the need to optimize calorie intake in the patient's sample. It is recommended that the enteral feedings for premature infants should be in the range 120-165 kcal/kg/day[34] and PN in the range 100-120 kcal/kg/day.[10] The maximum average cumulative intake by combined nutrition and PN in this study was 92.2 and 78.6 kcal/kg/day respectively. The recommended nutritional intake for premature neonates is 125 kcal/kg/day in order to achieve similar intra-uterine growth, 15 g/kg/day of weight gain, 0.5-0.8 cm per week of head circumference growth and 0.8-1.1 cm per week of body length growth.[6] An intake of AA between 2.3-2.65 g/kg/day is required to achieve a positive nitrogen balance.[10] It is important to adhere to the above criteria since growth restriction in premature infants is a morbidity which will affect their growth and development.[7] Olsen and Richardson concluded that nutrition was the most important explanatory factor for the variations in growth differences in their study.[34]

The results of this study strongly suggest, therefore, that the current practice regarding the administration of PN to premature neonates in this hospital needs to be reviewed in order to optimize the desired outcomes. The limitation of this study is that it was carried out retrospectively and with a relatively small number of neonates in each of the age groups. Other confounding factors that could influence the development of VLBW infants, such as lipid and EN supplementation or the different genetic backgrounds (ethnicity) of the neonates were not controlled in this study.

Conclusion

This study identified that in a local hospital setting, where PN is provided, there is a possibility that current nutritional practices for VLBW infants are inadequate to achieve the standard growth recommendations. These findings call for a need to increase the AA dosing from the current range of 0.5-2.5 g/kg/day since growth restriction is a morbidity which will affect the infants'

growth and development. In addition, this study sets the stage for larger clinical trials on the effect of early, higher amino acid intake on duration of hospitalization, short- and long-term postnatal growth, and neuro developmental outcomes.

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AUTHOR DISCLOSURES

No competing interests are reported.

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Original Article

Amino acid dosing in parenteral nutrition for very low birth weight preterm neonates: an outcome assessment

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极低出生体重早产儿肠外营养中氨基酸的剂量效果评价

本研究旨在马来西亚当地一家医院进行回顾性研究，探讨极低体重儿肠外营养（PN）氨基酸（AA）对体格改变的影响。在 2012 年间，从新生儿病房登记的新生儿记录中按规定筛选出合格的新生儿，一共有 199 名早产儿接受 PN 支持，其中 100 名符合纳入标准。早产儿第一天肠外营养 AA 摄入量的中位数是 2.00（<28 周组）、1.00（28-31 周组）和 0.75（>31 周组）。与其他两组相比，<28 周组早产儿更容易在较早的时间接受较高的初始 AA 剂量。本研究还发现 PN 管理的第一天 AA 的使用剂量没有统计学差异，而且受试者营养参数的显著差异并没有导致生理结果的差异。本研究确定了在当地医院环境下提供 PN 的时间，很有可能目前的营养做法不足以达到早产儿标准生长建议。由于增长限制的发病率会影响婴儿生长发育，我们的研究结果呼吁需要优化 AA 和热量的摄入量。为了改善患者的治疗效果，需要对这家医院当前的 PN 处方进行审查。

关键词：出生体重、营养需求、生长发育、营养支持、营养治疗