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The Influence of Aggressive Parenteral Nutrition to Preterm and Very Low Birth Weight Infants

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Abstract

Background. To achieve the weight gain of preterm infants who are appropriate for gestational age without adverse effect, there should be no interruption in delivery of nutrients from time of birth. *Methods*. Twenty-eight very low birth weight infants were eligible for the study. Those administered conventional nutrition (amino acids 2 g/kg/day started on third day of life) were classified as the conventional support (CVS) group, and those administered aggressive early nutrition (amino acid 2 g/kg/day started on first day of life) were classified as the aggressive support (AGS) group. *Results*. The days babies took to reach the weight of 2000 g in the AGS group was significantly shorter than for babies in the CVS group, and babies in the AGS group showed better tolerance to enteral nutrition and had shortened neonatal intensive care unit days. *Conclusion*. The results demonstrated that aggressive early nutrition showed better tolerance to enteral nutrition, higher total calories, and shortened the stay in the neonatal intensive care unit.

Keywords

very low birth weight infant, parenteral nutrition, postnatal growth

Introduction

Infants born at less than 1500 g weight are defined as having very low birth weight (VLBW). These infants are often born less than 37 weeks gestational age in the intrauterine period of brain and rapid body growth.[1] The postnatal nutrition in preterm infants is designed to mimic the growth and body composition of the healthy fetus growing in the uterus. Some recent evidence has demonstrated that inadequate nutrition in premature infants in the first week results in growth retardation and may lead to permanent detrimental effects.[2,3] Malnutrition is a cause of morbidity and mortality in VLBW infants receiving less nutrition in the first week of life. Therefore, parenteral nutrition (PN) is required until full enteral nutrition can be established.[4] Now that the survival rates of VLBW infants have improved with use of mechanical ventilation and exogenous surfactant,[5] preterm infants are faced with another challenge in nutrition. Extrauterine growth retardation is associated with adverse outcomes including chronic lung disease, increased risk to infection, severe retinopathy, and abnormal neurodevelopment outcome.[6-8]

To achieve weight gain of preterm infants who are appropriate for gestational age without adverse effect, there should be no interruption in delivery of nutrients from time of birth. There should be use of adequate PN to minimize weight loss and improve growth outcome. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recommended a caloric intake of 110 to 135 kcal/kg/day for children enterally fed and 110 to 120 kcal/kg/day for those parenterally fed, with a protein intake of 3.5 to 4 g/kg per day.[9,10] It is difficult for most VLBW infants to reach this suggested caloric and protein intake because of fluid restriction, intolerance to suggested glucose infusion rate, delay in initiation of parenteral amino acid solutions, immaturity of intestinal functions, and slow progress of enteral feeding.

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Recent studies have reported that an aggressive approach of starting amino acid administration at a dosage of 3 g/kg/day beginning within the first 24 hours of life is an effective method of improving weight gain and anabolism.[11-13] ESPGHAN has recommended that, in newborn infants who cannot receive sufficient enteral feeding, intravenous lipid emulsions should be started no later than on the third day of life but may be started on the first day of life.[10] Despite this, in Taiwan premature infants are often discharge at weighs less than the 10th percentile and with more complications. These infants receive parenteral nutrition in keeping with the then current unit policy. Amino acid solution was started at 1 g/kg/day on the third day and increased by 0.5 g/kg/day to a maximum of 2.5 g/kg/day. Lipid emulsions were started after the third day of life.

This retrospective study evaluated the effect of amino acid administered on the first day and lipid emulsions started on the second day of life in VLBW infants (aggressive early nutrition policy) compared with amino acid solution administered on the third day and lipid emulsions started after the third day of life in VLBW infants (conventional nutrition policy).

Materials and Methods

Subjects

Preterm infants (born from 2010 to 2012) with a birth weight of <1500 g and more than 750 g were eligible for the study. From 2010 to 2011, we implemented the conventional nutrition policy, since 2012 we changed to an aggressive early nutrition policy to preterm and VLBW infants. Infants were excluded if they had major congenital anomalies, were less than gestational age 23 weeks, and died within 5 days of birth. Patients' data acquisition and subsequent use were approved by the institutional review board of the Tainan Sin-Lau Hospital (Grant No. SLH919-102-11). There was no funding source relevant to the study.

Fifteen preterm and VLBW infants included from 484 infants who were admitted to the neonatal intensive care unit (NICU) from January 2010 to December 2012 were classified as the conventional support (CVS) group, and 13 preterm and VLBW infants included from 156 infants who were admitted to the NICU in 2012 were classified as the aggressive support (AGS) group.

Nutrition Administration and Classification

These infants received fluids started at a rate of 80 mL/kg/day and increased to 150 mL/kg/day when patent ductus arteriosus closed. On admission to the NICU, these infants received parenteral nutrition, 4 mg/kg/min of glucose, during the first 24 hours of life. The glucose infusion was increased progressively to a maximum of 6 mg/kg/min to maintain blood glucose levels less than 120 mg/dL. The infants who started on amino acids on the third day of life were classified as CVS group, or AGS group if amino acid was started on the first day of life, 10% amino acid solution (Aminosteril Infant Fresenius Kabi, Germany) at a rate of 2 g/kg/day and increased by 0.5 g/kg/day until a total of 3 to 4g/kg/day was reached without renal failure or metabolic acidosis. A 20% lipid solution, which is an equal mixture of medium-chain triglycerides and long-chain triglycerides (Lipofundin, B Braun Ltd), was introduced in the CVS group after the third day of life and in the AGS group on the second day of life (after peripherally inserted central catheter) at 0.5 g/kg/day and increased by 0.5 g/kg/day until 3 to 3.5 g/kg/day was reached.

Parenteral nutrition was maintained until enteral feeding reached 100 mL/kg/day. The CVS group received enteral feeding on day 3 with breast milk or half-strength preterm formula (about 12 kcal/oz or even less) at 10 mL/kg/day. The AGS group received enteral feeding on day 3 of life or as soon as possible, with breast milk or preterm formula (22 kcal/oz) at 10 mL/kg/day. Feeds were increased by 10 mL/kg/day during the first 7 days of life, and by 15 to 20 mL/kg/day thereafter until the rate reached more than 150 mL/kg/day. In the presence of progressive gastric residuals or abdominal distension, the volume of feeds was reduced.

Clinical Outcomes

The infants' weight gain was recorded weekly. The clinical outcomes were predefined as below. Chronic lung disease was defined as the need for supplemental oxygen at 28 days, and bronchopulmonary dysplasia (BPD) as the need for oxygen at 28 days with classic chest radiographic changes. Necrotizing enterocolitis (NEC) was confirmed by the presence of gas or air bubbles in the wall of the intestine on an abdominal X-ray. A patent ductus arteriosus (PDA) diagnosed on echocardiography was considered clinically significant when it required ligation. Intraventricular hemorrhage (IVH) grade II or higher was according to the classification of Papile et al.[14] Cystic periventricular leukomalacia (cPVL) was diagnosed on cranial ultrasonography. Retinopathy of prematurity (ROP) was defined according to indirect ophthalmoscopy.

Statistical Analysis

Two-sample *t* tests were used to measure differences in clinical outcomes between the 2 groups of infants. The

Table 1. Clinical Characteristics.

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Weeks of gestation, mean ± SD	29.0 ± 1.5	29.7 ± 2.0	NS
Birth weight (g), mean ± SD	1144.0 ± 231.4	1262 ± 132.2	NS
Cesarean section, n (%)	6 (40)	7 (53)	NS
Ventilated, n (%)	4 (26.6)	4 (30.8)	NS
Apgar score/5 min, mean ± SD	8.1 ± 0.78	8.0 ± 0.76	NS

Abbreviation: NS, not significant.

Table 2. Nutritional Intake and Stay in the NICU.

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Age enteral feeds started (days), mean ± SD	7.07 ± 5.2	5.07 ± 2.5	.21
Parenteral nutrition (days), mean ± SD	32 ± 16.4	21.5 ± 9.8	.13
Infants' stay in NICU (days), mean ± SD	30.1 ± 14.3	19.31 ± 10.0	.04*

Abbreviation: NICU, neonatal intensive care unit.
*$P < .05$.

Table 3. Anthropometry Data and Days Taken for Infants to Grow to 2 kg [a].

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Weight (g)			
Day 1	1144.0 ± 231.4	1262 ± 132.2	.139
Week 1	1030.2 ± 238.1	1156.2 ± 157.8	.153
Week 2	1138.0 ± 278.5	1311.8 ± 196.2	.102
Week 3	1291.9 ± 314.3	1521.0 ± 243.8	.066
Week 4	1477.3 ± 346.0	1746.7 ± 260.2	.048*
Head circumference (cm)			
Day 1	26.3 ± 1.4	26.6 ± 1.6	.714
Week 4	29.3 ± 1.2	30.0 ± 1.1	.196
Infants growth up to 2 kg, hospital days	43.9 ± 17.4	32.2 ± 11.0	.047*

[a]Data are presented as mean ± SD.
*$P < .05$.

Wilcoxon signed-rank test was used to analyze differences in the measurements without normal distribution. Categorical data were analyzed using χ^2 test and Fisher's exact test. Statistical analysis was done using SPSS 17.0 (SPSS, Chicago, IL).

Results

A total of 28 preterm infants with birth weight between 750 and 1500 g admitted at our NICU were enrolled during the period—January 2010 through December 31, 2012. Babies were divided into 2 groups: 15 preterm infants (9 males) included in the CVS group and 13 preterm infants (4 males) in the AGS group. There were no differences in demographic or baseline characteristics between the 2 study groups (Table 1).

There was no significant difference in total days of parenteral nutrition received between the 2 groups. The AGS group had earlier initiation time to enteral feeding; however, there were no significant differences in the data. However, stay in the NICU was shorter for infants in the AGS group than in the CVS group (19.31 ± 10.0 vs 30.1 ± 14.3, $P = .04$; Table 2).

There was no significant difference in both groups with regard to loss in birth weight in the first week. But the weight gain at the fourth week in the AGS group was significantly more than in the CVS group ($P < .05$). The days taken for the babies reach a weight of 2000 g in the AGS group was significantly shorter than in the CVS group (32.2 ± 11.0 vs 43.9 ± 17.4, $P = .047$; Table 3).

The growth of preterm infants with aggressive early nutrition policy was better than in the conventional group.

Table 4. Weight Change Compared With Birth Weight[a].

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Week 1 (g)	−113.8 ± 49.8	−108.9 ± 124.2	.900
Week 2 (g)	−5.2 ± 84.3	46.7 ± 142.3	.294
Week 3 (g)	161.4 ± 112.3	255.9 ± 183.9	.161
Week 4 (g)	333.3 ± 144.1	481.6 ± 205.9	.057

[a]Data are presented as mean ± SD.

Table 5. Weight Change Compared With First Week Weight[a].

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Week 2 (g)	108.7 ± 67.4	155.6 ± 52.5	.078
Week 3 (g)	261.8 ± 103.6	364.8 ± 101.3	.025*
Week 4 (g)	447.1 ± 136.8	590.5 ± 115.0	.013*

[a]Data are presented as mean ± SD.
*$P < .05$.

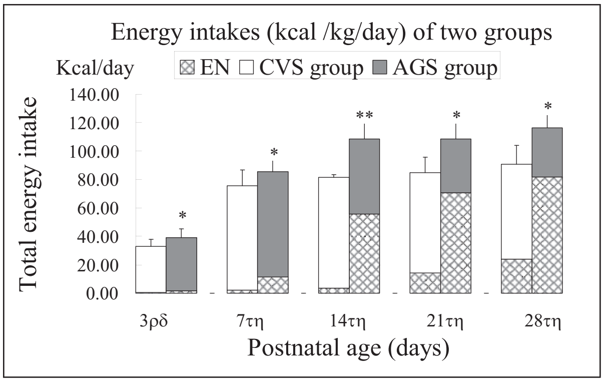

Figure 1. Mean total enteral and parenteral energy intakes (kcal/kg/day) in the 2 groups.
Data are expressed as mean ± SD. Single asterisk (*) indicates $P < .05$; double asterisk (**) indicates $P < .001$. Grid columns expressed as enteral nutrition of 2 groups. White columns express parenteral nutrition of the CVS group, gray columns show parenteral nutrition of the AGS group.

We checked weight change of both groups compared with their birth weight. However, there were no significant differences to weight change in both groups (Table 4), but we found there was a trend to better postnatal growth in the AGS group. We further compared the differences of weight change at the second, third, and fourth weeks with the first week. The results showed in the AGS group weight gain in the third and fourth weeks was significantly higher than in the CVS group (Table 5).

Total energy intake (enteral and parenteral) of each group is shown in Figure 1. There was significantly higher ($P < .05$) mean energy intake achieved in the AGS group at all time periods while receiving parenteral nutrition (Table 6). Amino acids were infused earlier in the AGS group; the intake of total amino acids was higher ($P < .05$) in the AGS group from the third day to third week. Total lipid intake from the second week to fourth week in AGS group was significantly higher than in the CVS group ($P < .05$).

Table 6. Total Energy, Amino Acid, and Lipid Intake of Enteral and Parenteral Nutrition[a].

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
Energy (kcal/kg/day)			
Third day	32.8 ± 5.2	39.0 ± 6.3	.020*
Week 1	75.5 ± 11.2	85.5 ± 8.4	.047*
Week 2	81.6 ± 1.8	108.6 ± 13.1	<.001**
Week 3	84.8 ± 11.0	108.6 ± 14.4	.001*
Week 4	90.8 ± 13.3	116.2 ± 14.4	.001*
Amino acid (g/kg/day)			
Third day	0.02 ± 0.03	0.8 ± 0.7	.010*
Week 1	2.5 ± 0.6	3.1 ± 0.4	.038*
Week 2	3.0 ± 0.3	3.5 ± 0.4	.047*
Week 3	3.0 ± 0.3	3.3 ± 0.2	.043*
Week 4	3.0 ± 0.5	3.3 ± 0.2	.157
Lipid (g/kg/day)			
Third day	1.9 ± 0.21	2.0 ± 0.4	.532
Week 1	3.75 ± 0.53	4.03 ± 0.44	.282
Week 2	3.88 ± 0.09	5.2 ± 0.73	<.001**
Week 3	3.87 ± 0.34	5.33 ± 0.84	<.001**
Week 4	4.23 ± 0.57	5.74 ± 0.87	.001*

[a]Data are presented as mean ± SD.
*$P < .05$. **$P < .001$.

The clinical outcomes between the 2 groups are summarized in Table 7. There was no significant difference between the 2 groups in terms of morbidity and duration of hospitalization.

Discussion

Weight loss in the first week of life is a common condition for preterm infants. The data from Tables 4 and 5 show that aggressive nutritional avoided excessive body weight loss in the first and even in the second week. There was no significant difference in the 2 groups when comparing the birth weight at 4 weeks, but when we further compare

Table 7. Clinical Outcomes.

	CVS Group (n = 15)	AGS Group (n = 13)	*P*
BPD	1	1	NS
NEC	0	0	NS
PDA	0	0	NS
IVH	0	0	NS
Late-onset sepsis	0	0	NS
ROP	1	1	NS

Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; NS, not significant.

the weight difference between the first weeks, we found the weight gain in the third and fourth weeks in the AGS group was significantly higher than in the CVS group. Valentine et al reported that early amino acid administration begun before 24 hours of life, in preterm infants, <1500 g, improves preterm infant weight.[15] Despite there being no significant difference in the total days parenteral nutrition received, in the present study we see that enteral nutrition has a higher proportion of total calories in the AGS group (Figure 1). This means that aggressive the early nutrition group has better tolerance to enteral nutrition, higher total calories, and shortened NICU time.

Aggressive early intravenous amino acid in VLBW babies can lower protein breakdown, promote positive nitrogen balance, and increase protein synthesis.[3,16,17] Dinerstein et al showed that early aggressive intervention of TPN and enteral feeding resulted in better growth in head circumference, weight and height, and an improvement of nutritional statuses at 40 weeks of gestation.[18] Our study showed that the early nutrition policy resulted in a significantly higher energy and protein intake without an increased incidence of adverse clinical outcomes. There were no differences in the head circumference in the fourth week.

Can et al reported that preterm infants receiving aggressive PN showed positively improvement in neonates' anthropometric measurements at the 40th gestational week and the development of ROP. These effects may be related to high levels of insulin-like growth factor-I (IGF-I) and IGF binding protein 3 (IGFBP3).[13] Weight loss of first week premature infants is a very common phenomenon. Our study showed that an aggressive early nutrition policy can reduce the weight loss of VLBW infants in the first week, and therefore the hospital days of babies' weight to 2000 g in the AGS group was significantly shorter than in the CVS group.

Aggressive early parenteral nutrition provided a decreased loss of amino acids in premature infants on the first day of life.[16] In premature infants receiving PN, an amino acid intake of 3.5 to 4.0 g/kg/day and 120 kcal/kg/day was needed to meet the intrauterine accretion rate.[19,20] Despite our efforts meet the recommendations we still cannot avoid deficits in energy and proteins intake until after 2 weeks.

Taiwan's birth rate is one of the lowest in the world. The birth rate in Taiwan is now below the rate needed to sustain population growth. It is important to speculate whether this improved early growth could influence the long-term neurological, renal function, and cardiovascular disease outcomes. A follow-up on the infants included in this study is needed to evaluate neurodevelopmental outcome, metabolic abnormalities, and systemic disease and subsequently to avoid the temptation to "fatten-up" an otherwise healthy preterm baby.[21]

Conclusions

The results demonstrated that an aggressive early nutrition policy showed better tolerance to enteral nutrition, higher total calories, and shortened the NICU days. Our finding was that infants subjected to an aggressive introduction of parenteral nutrition and early feeding showed better tolerance to enteral nutrition and weight gain than those in the conventional group.

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Declaration of Conflicting Interests

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