보건학 석사 학위논문

The effect of standard versus high parenteral amino acid supplementation on growth and metabolic state in very low birth weight infants

출생체중 1.5kg 미만의 극소 저 체중 미숙아에서 생후 첫 2주간 아미노산 공급량에 따른 성장 및 대사상태 비교

2012년 8 월

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이 논문을 보건학 석사 학위논문으로 제출함

2012년 4월

서울대학교 보건대학원
보건학과 보건통계학전공
양 사 미

양사미의 보건학 석사 학위논문을 인준함
2012년 8월

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Abstract

The effect of standard versus high parenteral amino acid supplementation on growth and metabolic state in very low birth weight infants

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Objective: The purpose of the present study is to compare the effect of two, different strategies for early parenteral AA supplementation in the range of the standard dose of AA (>1.5 g/kg/day), on the short– and long–term growth parameters and other metabolic state in VLBW infants.

Design: Retrospective cohort study

Setting: Thirty eight-bed neonatal intensive care unit at Asan Medical Center, Korea.

Patients: We included 109 patients who admitted to NICU over a period of January 2008 to December 2009.

Methods: A chart review was done in a total of 109 VLBW infants hospitalized in our NICU from 2008 to 2009 if they had no major congenital anomalies or renal failure. During the study period, unit policy on the parenteral AA supplementation did not change except for the starting AA doses at the first day of life ; 1.5 g/kg/day (n=56, standard protein group, SP, in 2008) versus 3.0 g/kg/day (n=53, high protein group, HP, in 2009). The AA dose was advanced by 0.5 g/kg/day to a target maximum of 3.5 to 4.0 g/kg/day. Daily protein and non-protein energy intakes and chemical laboratory profiles were collected for the first 14 days of life. Outcome variables including mortality and neonatal morbidities during hospitalization and growth parameters at postnatal 14 days, 36 weeks', 6 months', and 12 months of corrected age(CA) were also collected.

Results: The baseline clinical characteristics between the 2 groups were similar. The mean protein intake during the first 14 days of life was greater in the HP group than SP group (2.9±0.4 vs. 2.6±0.4/kg/d; p<0.001). Mean non-protein

energy intake and amount of enteral protein intake did not differ between the 2 groups. There was no significant difference in the weight, length and head circumference at postnatal 14 day, 36 weeks', 6 months' and 12 months of CA between the HP and the SP groups. Peak plasma glucose level during the first 3 days of life was lower in the HP group than in the SP group (116.4±23.6 vs. 136.5±38.3 mg/dL, p=0.001), while mean serum blood urea nitrogen level was higher in HP group compared with SP group.

Conclusions: Early provision of higher dose of AA was well-tolerated without significant metabolic adverse effects. In the range of standard parenteral AA protocol, no dose-response relationship was observed between the AA doses and growth outcomes in VLBW infants.

Key words: amino acid, premature, growth, intensive care, parenteral nutrition

Student number: 2010-22103

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I. Introduction

Advancement of medical care has remarkably improved survival of preterm infants. Technological and pharmacological advances of the last 30 years, such as increased prenatal referral to tertiary centers, antenatal steroid administration for lung maturation, initiation of assisted ventilation at delivery, surfactant replacement therapy, new techniques of ventilation, and regionalization of perinatal care resulted in improvement of perinatal management[1]. As a result, a substantial increase in survival of infants born mainly at extremely low gestational ages (< 28 weeks) has occurred[2]. However, as increasing more immature preterm infants survive, challenges related to providing preterm infants, especially very low birth weight (VLBW) infants, weighing less than 1,500g of birth weights, with optimal nutrition for growth and development have become daunting. Despite advance in perinatal medicine and nutritional protocols, growth in preterm infants hospitalized in the neonatal intensive care unit (NICU) is slower than that of intrauterine growth for same gestation infants[3-5]. Extrauterine growth restriction (EUGR, <10th percentile for gestational age) is associated with an increased risk of poor neurodevelopmental outcomes[6-9], and inappropriate postnatal nutrition is an important contributor to growth failure[10,11]. As stated recently

by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) committee, the goal for premature infants is obtaining a functional outcome comparable to infants born at term[12]. Thus, it is crucial to optimize neonatal nutrition in a way that unhampered brain growth and development is stimulated [13].

1. Extrauterine Growth Restriction (EUGR) and nutrition

Poor in-hospital growth is the most frequent morbidity in VLBW population. According to Lemons et al.[14], EUGR was presented in 97% of the VLBW infant. EUGR occurred in 100% of infants born at 501 to 750 g, 98% of infants born at 751 to 1000 g, 97% of infants born at 1001 to 1250 g, and 95% of infants born at 1251 to 1500 g. Although EUGR has been present for a long time, few studies have evaluated the efficacy and safety of multiple interventions to prevent or decrease EUGR rates at discharge in VLBW infants[15]. Growth is influenced by many factors, such as genetic background, hormones, nutrition, and environment(Fig 1)[16], and inadequate nutrition has long been suspected to be major cause of the EUGR[17].

As mentioned above, the major problems of EUGR is an

association of developmental outcome with slow growth during neonatal period and are particularly important from a nutritional point of view[18-21]. Since growth and development of the central nervous system are particularly rapid during the third trimester of gestation, it seems reasonable to assume that the impact of inadequate nutrition during any part of this period is likely to detrimental.

In a number of observational studies, a relationship between slow weight gain and low protein intake among premature infants has been documented[11,22-26]. And these reports show that protein intakes are considerably did not reach the requirements, though energy intakes were close or even above requirements. In 2009, Stephens et al.[27] demonstrated that increased first-week protein and energy intakes are associated with higher mental development index(MDI) scores and lower likelihood of length growth restrictions at 18 months. These findings have provided the major impetus for the adoption of vastly improved parenteral nutrition regimens in the days immediately following birth.

2. Effects of nutrition on metabolic health in prematurity

Recent investigations have shown the early origins of

metabolic syndrome to be associated with prematurity. Barker emphasized that differences in nutritional experiences during sensitive periods in early life, both before and after birth, can program a person's future development, metabolism, and health[28]. Other studies reported that children who were born prematurely had an isolated reduction in insulin sensitivity[29], and that a high carbohydrate and lower protein neonatal diet could lead to greater weight gain and a greater reduction in insulin sensitivity in preterm infants[30]. One randomized controlled trials demonstrated a causal relation between nutrition in infancy and later outcomes, including cognitive function and cardiovascular risk factors[31]. Moreover, the evidence led to conclusion that early nutritional environment interacts with an individual's genetic disposition to program metabolism and development. Meanwhile, they also reported that relative under-nutrition early in the life in children (13 to 16 years of age) who were born prematurely may have beneficial effects on insulin resistance and cardiovascular disease (CVD) risk. However, malnutrition may be likely to develop neurological impairment or short stature as well as metabolic syndrome and CVD. These findings make clinicians to face a dilemma with respect to the nutrition of preterm infants. Therefore, preterm infants must be fed the right amount, at the right time and early aggressive nutrition should be initiated

after birth not only to supply essential amino acids and fatty acids, but also to prevent starvation response; nutrient requirements change with development and gestational age.

3. Amino acids (AA) supplementation in VLBW infants

During the immediate newborn period, sick infants, especially preterm infants, may not tolerate standard amounts of nutrients normally delivered to clinically stable infants and may not tolerate adequate energy intakes for optimal utilization of AA. The administration of glucose alone may result in hyperglycemia and cannot fully prevent tissue catabolism, and early administration of protein as amino acids may decrease the risk for hyperglycemia and promote nitrogen retention[32].

During the early days following the birth of preterm infants, parenteral nutrition (PN) must replace the role of the placenta by providing a continuous supply of nutrients and minerals in order to fulfill the nutritional needs of growing fetuses. Although providing doses of macronutrients similar to those of placental transfer can be achieved with currently used method of neonatal PN, the optimal dose of AA which are the major building blocks for the growth of preterm infants, have been the topic of studies regarding the nutritional management of the

very low birth weight (VLBW) infants. A linear relationship between AA intake and nitrogen retention in both fetuses and neonates was revealed and a minimum intake of 1.0 to 1.5 g/kg/d of AA has been recommended as the "standard dose" of early AA in PN in order to prevent a negative nitrogen balance[33]. However, this level is far from the AA dose of fetal transfer that can approximate ideal protein accretion and fetal growth. At least in part, EUGR may be attributable to the gap between the "standard dose" of AA in PN and those of the "fetal dose" (3.5 to 4.0 g/kg/day) during the early days after birth.

Analysis of data from studies published before 1986 showed that weight gain (g/day) increases with linearly with increasing protein intakes up to about 4.2 g/kg/day[34,35]. The authors estimated that AA requirements weighing > 1,200g to grow like the fetus was about 3.0 g/kg/day. This value is similar to values derived from observational studies. In the study by Olsen et al.[23] a single gram per kilogram of a single gram per kilogram of additional protein was associated with an increment of weight gain of 4.1 g/kg/day and in the study by Ernst et al.[24], each gram per kilogram of protein was associated with weight gain of 6.5 g/day (equivalent to 4.3 g/kg/day if weight is assumed to be 1.5 kg). A randomized controlled trial by Poindexter et al.[36] revealed that infants provided ≥ 3 g/kg/day of AA at ≤ 5

days life had significantly better growth outcome at 36 weeks' corrected aged in extremely low birth weight(ELBW, < 1,000g of birth weight)infants without distinct adverse effects.

Despite concerns regarding the negative influence of an excess level of some AAs and/or their metabolites on premature infants, the metabolic safety of the administration of the fetal dose of AA during the early neonatal period has been studied even in extremely low birth weight infants with limited metabolic and excretory capacity[37]. Based on the above evidences, Ehrenkanz[38] established a recommendations and evidence quality on early nutritional practice including AA administration for VLBW infants (Table 1)[39] according to the quality of the available evidence, as defined in a policy statement by the American Academy of Pediatrics[39]. However, there are still conflicts regarding whether early and higher doses of AA administration in VLBW infants can translate into better outcomes in terms of their growth[40]. There have been a few studies demonstrating the benefit of a higher AA supplement on neonatal growth[41-43], however, little is known regarding the effect of the fetal dose of AA administration in premature infants on their long-term growth outcome.

II. Objective

Provision of parenteral amino acid (AA) at the first day of life is now a widely accepted nutritional practice in the management of very low birth weight (VLBW) infant. However, it is not determined whether early and higher AA supplementation can translate into the better growth outcomes. The purpose of the present study is to compare the effect of two different parenteral AA supplementation strategies (targeted dose of 1.5 g/kg/day versus 3.0 g/kg/day at the first day of life) on the short- and long-term growth parameters in VLBW infants. Furthermore, we examined that higher AA administration would be associated with metabolic beneficial effects and/or other complications. It was hypothesized that infants who received high protein intakes in early days of life would have better growth outcome without distinct adverse effects.

III. Methods

1. Study Subjects

All newborn infants who were born at Asan Medical Center between January 2008 and December 2009, and with birth weights < 1,500g and gestational ages between 24+0 weeks and 33+6 weeks and who survived and were discharged after 36 weeks of corrected age(CA), were enrolled. Exclusion criteria included infants with major congenital anomalies or acute renal failure (serum creatinine ≥ 1.6 mg/dL) and in whom the AA supply was restricted during the early neonatal period so as to avoid a higher urea nitrogen level.

2. Nutritional management

From January to December 2008, parenteral AA was started at a rate of 1.5 g/kg/d for all VLBW infants from the first day of life (mostly within the first hour of life) (standard protein, SP, group). Meanwhile, beginning in January 2009, the unit policy regarding the AA dose on the first day of life, was changed to 3.0 g/kg/d (high protein, HP, group). AA was administered as a standardized preparation in a premixed bag containing 10% dextrose with 2.2% and 4.4% AA concentration for the SP and HP groups, respectively. From the second day of life, the AA

dose was increased in the form of an individualized PN solution. The unit policy regarding the increasing rate (by 0.5–1.0 g/kg/d) and the target amount (3.5–4.0 g/kg/d) of AA in VLBW infants, did not differ between the two groups(Table 2). Fluid intake was restricted to 70–80 mL/kg/day on the first day of life and thereafter it was generally increased by 10–20 mL/kg/day, reaching 130–140 mL/kg day at 10–14 postnatal days by monitoring the body weight, serum sodium, and urine volume. Except for the AA doses, there were no differences in the other nutritional strategies for parenteral (dextrose, lipid and minerals) and enteral nutrition between the two periods; and dextrose was administered to maintain the serum blood glucose between 80 and 180 mg/dL in an effort to avoid hyperglycemia (serum glucose concentration > 200 mg/dL) when the hyperglycemia was managed with a decreasing glucose infusion rate and/or intravenous insulin. Intravenous lipid emulsion was initiated on the second day of life at a rate of 0.5 g/kg/day and was increased by 0.5 to 1.0 g/kg/day to maintain a target of 3.0 g/kg/day. Enteral feeding was initiated as trophic feeding with breast milk or, if not available, with preterm formula once the infant was considered to be able to tolerate enteral feeding. As enteral feeding was advanced, the amount of intravenous fluid and, accordingly, the dose of AA decreased. When the infant fed with breast milk could tolerate

100 mL/kg/day of enteral feeding volume and was at least after two weeks old, human milk fortifier (HMF®, Maeil, Korea) was mixed with their mothers' milk in the patients fed with breast milk. PN supplementation was stopped when feedings reached 130 to 140 ml/kg/day. All patients were discharged fed with PM or fortified BM or both, but the detailed data regarding the post-discharge formula could not be investigated.

3. Data collection and monitoring

Data were collected using an electronic medical records system. Demographic parameters and perinatal data including the use of antenatal steroid, APGAR scores, and CRIB II scores, were obtained. Other outcomes of the neonatal mortality and morbidities which could affect their growth, were also obtained and included: respiratory distress syndrome, bronchopulmonary dysplasia (defined as oxygen requirement at the CA of 36 weeks); indomethacin treatment of patent ductus arteriosus (PDA); PDA ligation; early- or late- onset sepsis (defined as identification of bacteria or fungus cultured in the blood or cerebrospinal fluid within or after seven days of life, respectively); severe-grade (Grade 3 or 4 by Papille classification) intraventricular hemorrhage; retinopathy of prematurity requiring laser therapy; necrotizing enterocolitis or intestinal perforation that required surgical and PN-associated

cholestasis (direct bilirubin > 2.0 mg/dL) and the days of oxygen supplement; mechanical ventilator therapy; and hospitalization. Detailed data regarding the nutritional management were collected from an electronic nutritional chart program developed by our unit. In this program, the daily amount and calories provided by each major nutrient were automatically calculated from the individualized PN and enteral feeding orders which were confirmed or modified by a neonatal pharmacist. Actually administered doses (g/kg/d) of AA and the total and non-protein calories (kcal) administered both parenterally and enterally, were calculated during the first 14 days of life. In order to evaluate the tolerability and adverse effects of AA intake, the BUN, serum creatinine, bicarbonate, base deficit, blood sugar level, and potassium level were also obtained.

During hospitalization, body weight was measured daily using digital scales accurate to 10 g. Height and head circumference were measured weekly and at 36 weeks of CA age using a fixed head board and movable foot board and with a non-stretchable tape at the maximal occipitofrontal circumference. Weight, height, and head circumferences were compared with the latest intrauterine reference values[7] using z scores. As our unit has a routine clinic visit program for all VLBW infant survivors, the infants were followed at least every month until 6 months of CA

age and thereafter at least every two months till 12 months of CA. The growth profile was measured by calculating the z score change from birth to 36 weeks, 6 months, and 12 months of CA.

4. Statistical analysis

All analyses were performed using SPSS version 12 (SPSS, Inc, Chicago, IL, USA). Normally distributed data were presented as mean values with SD, and the patient groups were compared using a t-test. Non-normally distributed data are presented as the median value with a range and the groups were compared using the Mann-Whitney test. Categorial data are presented as actual numbers or percentages, and the groups were compared by the chi-square test.

Univariate and stepwise multivariate analysis were used to evaluate the influence of the clinical characteristics and the AA intake of growth expressed as z-score changes from birth to each time when the growth data was assessed.

The relationship between AA intake and serum BUN level was determined using Pearson's correlation coefficient (r or r^2). The results were considered significant if $p < 0.05$.

IV. Results

After discharge, 9 infants died within 12 months (n=5 in the SP group vs. n=4 in the HP group), and 19 infants (n= 11 in the SP group vs. n = 8 in the HP group) were lost to follow-up. Finally, a total of 109 patients were included in the study analysis (Figure 2).

Demographic and perinatal data did not differ in the two study groups (Table 3). The HP group received 11% more AA intake than the SP group for the first two weeks, and this was mostly due to the difference in the AA intake during the first week of life (Figure 3). The total amount of AA did not reach the target requirements (3.5-4.0 g/kg/d) till at the end of the initial 14 days after birth, because of the slow advance in parenteral and enteral feeding volume than we planned. There were no differences in the fluid volume, non-protein intake or enteral intakes between the study groups. The proportion of infants fed with preterm formula or fortified BM also did not differ between the two study groups during hospitalization (Table 4). The mean and peak BUN levels during the first two weeks of life were higher in the HP group (Figure 4), although the incidence of BUN > 40 mg/dL did not differ between the two groups. The mean and peak serum potassium and glucose levels and the incidence of hyperkalemia and hyperglycemia also did not differ

between the two study groups (Table 5). However, during the first three days of life, the peak blood glucose level was significantly lower in the HP group than in the SP group (P = 0.001). During the first three days of life, a linear regression analysis revealed a significant correlation between the AA intake and the mean glucose level, while adjusting for gestational age (r^2=0.248, P=0.009) (Figure 5).

There were no differences in the percentage of weight loss from birth weight and in the days required to regain birth weight between the SP and the HP groups. The proportion of the patients who regained their birth weight after two weeks of life also did not differ between the two study groups (Figure 6). There were no differences in the neonatal morbidities (Table 6).

In terms of the z-score change from birth to postnatal 14 days and 36 weeks, 6 months and 12 months CA, the changes in all of the growth parameters did not differ between the two groups (Figure 7). Multivariate analysis revealed that the z-score of the weight, height, and head circumference changes from birth to CA 36 weeks, could be explained by gestational age, the z-score at birth, duration of hospitalization, and the CRIB II score at birth. However, the mean AA intake during the first 14 days of life was not a determinant of any change in growth parameters at CA 36 weeks (Table 7). Likewise, the z-score

changes of the growth parameter from birth to 6 month and to 12 months were not correlated to the mean AA intake.

V. Discussion

In the present study, administration of a higher dose of AA in the VLBW infants, approximating the fetal AA transfer rate from the first day of life, did not result in better growth outcomes than in the group with the "standard dose" of AA.

Protein and energy intake meeting the recommended dietary intakes are rarely achieved in VLBW infants and they inevitably experience cumulative energy and protein deficits during the initial few postnatal weeks[33,37]. A dietary intake of protein of 3.0 g/kg/day or more from the first day of life is thought to prevent the interruption or reduction of the fetal dose of AA transfer and, thereby, theoretically can minimize postnatal growth restriction. Although several studies have addressed the effect of early and "aggressive" nutrition on the growth outcomes, most are observational studies and the effect of parenteral AA was not independently investigated.[36,40-43] Then, it is no wonder that most studies of nutritional interventions in preterm infants have been interested in the enteral feeding strategies rather than in early parenteral nutrition, with a different kind of enrichment protocol of AA and/or calories.[8,44-46]. Only a multicenter, randomized trial comparing two groups with different dosing strategies of parenteral AA, demonstrated a result similar to ours, in which the higher starting dose and

the faster advancement in the AA supplementation did not lead to better growth outcome at 28 days of age in the premature infants of < 30 weeks of gestation[40].

On the other hand, an observational study by Maggio et al., with a very similar design of nutritional strategies, including the AA dose, to ours, reported better height and weight gain in the higher AA group at the time of their hospital discharge[42]. In that study, the mean AA intake during the first two weeks of life was independently associated with weight and height z-scores in the short-term.

However, the intake of AA during the first two weeks of life did not correlate with the changes in the Z-scores of any of the growth parameters in our study.

The reasons for this discrepancy are unclear. However, our enrolled study patients were more mature (approximately 30 weeks vs. 27 weeks of gestational age) and the proportion of the small for gestational age (SGA) preterm infants was higher (30% versus 9%) than in Maggio's study. The effect of early AA intervention can be attenuated in the more mature infant group with faster achieving target enteral feeding and in SGA preterm infants with greater risk of postnatal growth retardation[47,48].

In our study, the metabolic benefit of higher AA supplementation was demonstrated in terms of serum glucose control, especially the peak blood glucose level was lower in the HP group during the first three days after birth(Table 4). Moreover, there was linear correlation of AA dose with mean serum glucose level during first three days of life(Figure 5), The increased concentration of the extracellular AA level, especially leucine, stimulates intracellular protein synthesis and suppresses protein breakdown, presumably by stimulating insulin secretion[49]. This insulin-dependent proteolysis suppression by AA has not been consistently documented in preterm infants previously[50,51], thus, our study would be a useful reference of dose-response relationship between AA and serum glucose level. Otherwise, several comparative studies composed of groups with different AA doses, failed to demonstrate the greater risk of hyperkalemia with a range of clinical concern in the group with the lower AA intake [32,42,52]. The metabolic benefit of early and higher AA infusion in a specific study group can be influenced by several factors such as the disease severity, patient maturity, and renal functions. As for the hyperkalemia, in particular, other factors such as exposure to antenatal corticosteroid treatment, can be relates to the early serum potassium levels[53 · 54]. However, these factors were comparable in our two study groups.

The clinical implication of a higher peak BUN level in our study's HP group is not clear. Even in this group, the mean peak BUN level was within the cord blood BUN range[55] and the proportion of patients with a peak BUN level over 40 mg/dL was also not greater than that seen in the SP group. No patients in either group demonstrated a serum BUN level > 60 mg/dL during the initial two weeks, and the advance in AA dose did not have to be stopped based solely on the serum AA levels. This may be due to the characteristics of the enrolled patients as those with acute renal failure had been excluded. Of course, there are still concerns regarding the potential risk of a high BUN and/or ammonia level in the developing brains of the extremely premature patient group[52]. However, until now, there has been no reliable evidence of a detrimental effect on the neurodevelopmental consequences caused by uremia of the degree commonly encountered during the early neonatal period in premature infants[37] The difference in the mean BUN level between our study groups might have resulted from the difference in the AA doses, although other investigators have failed to correlate the serum BUN levels with the amount of AA intake within three[56] or 15 days[57] after birth in more premature groups than those of our study.

There are some limitations to our retrospective study. First, as mentioned above, we did not reach the targeted total dose of AA because of the fluid volume restriction with other concomitant drugs' continuous infusion (e.g., inotropes, sedatives). Thus, the difference of the amount of AA had diminished than we planned, and it would be the reason two groups did not show significant difference in growth rates than we expected. Second, the influences of unexpected changes in the patient care other than nutritional factors could not be completely controlled, especially during the first two weeks after birth. However, factors potentially affecting the early growth rate, such as early neonatal morbidities and fluid management protocol, did not differ between the two study groups. Moreover, nutritional practices other than the AA doses did not change and were controlled and monitored by the same pharmacist. Third, nutritional strategies during the hospitalization and afterward up to the last time point of growth parameter could not be strictly regulated. However, the type of feeding formula did not differ between the two groups, although detailed data could not be obtained. Finally, the nutritional benefit (or risk) for the HP group over the SP group could not be evaluated in terms of nutritional quality. Lean body mass in preterm infants is less well-developed and the proportions of fat deposition could be affected by several factors such as the

disease severity[58]. Comparison analysis of the lean body mass in both groups using DEXA or MR fat imaging could clarify this issue.

VI. Conclusion

In conclusion, changes in nutritional practice by increasing the starting dose of AA from 1.5 to 3.0 g/kg/day and earlier achievement of the fetal dose of AA transfer, did not result in a better growth outcome in the VLBW infants assessed in our study. Further, well-controlled, prospective studies will be needed to determine the effect of early and higher AA intake on the quantity and the quality of growth in premature infants.

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Figure 1. Interaction between early diet and genes in defining relevant health and quality of life outcome. CHO, indicates carbohydrates (Data are from reference 16)

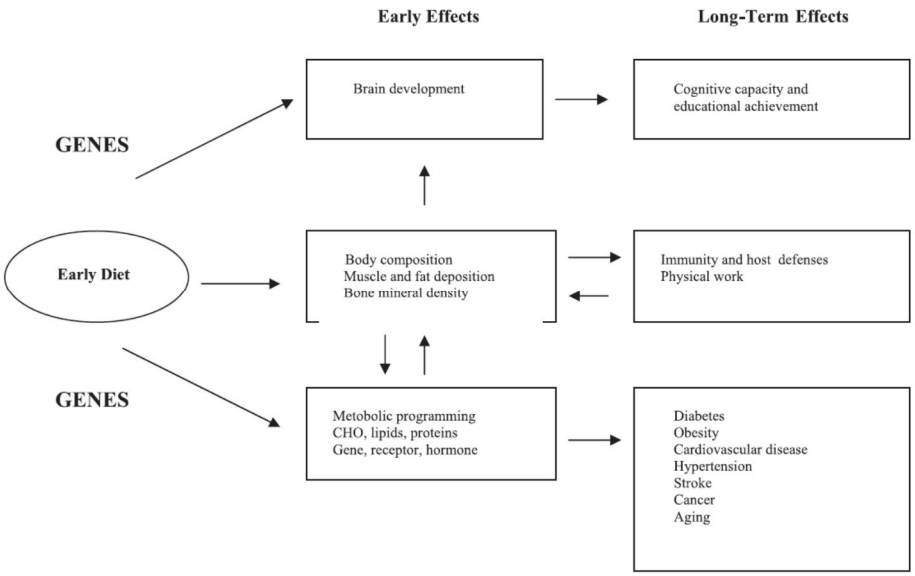


Figure 2. Flowchart of study population

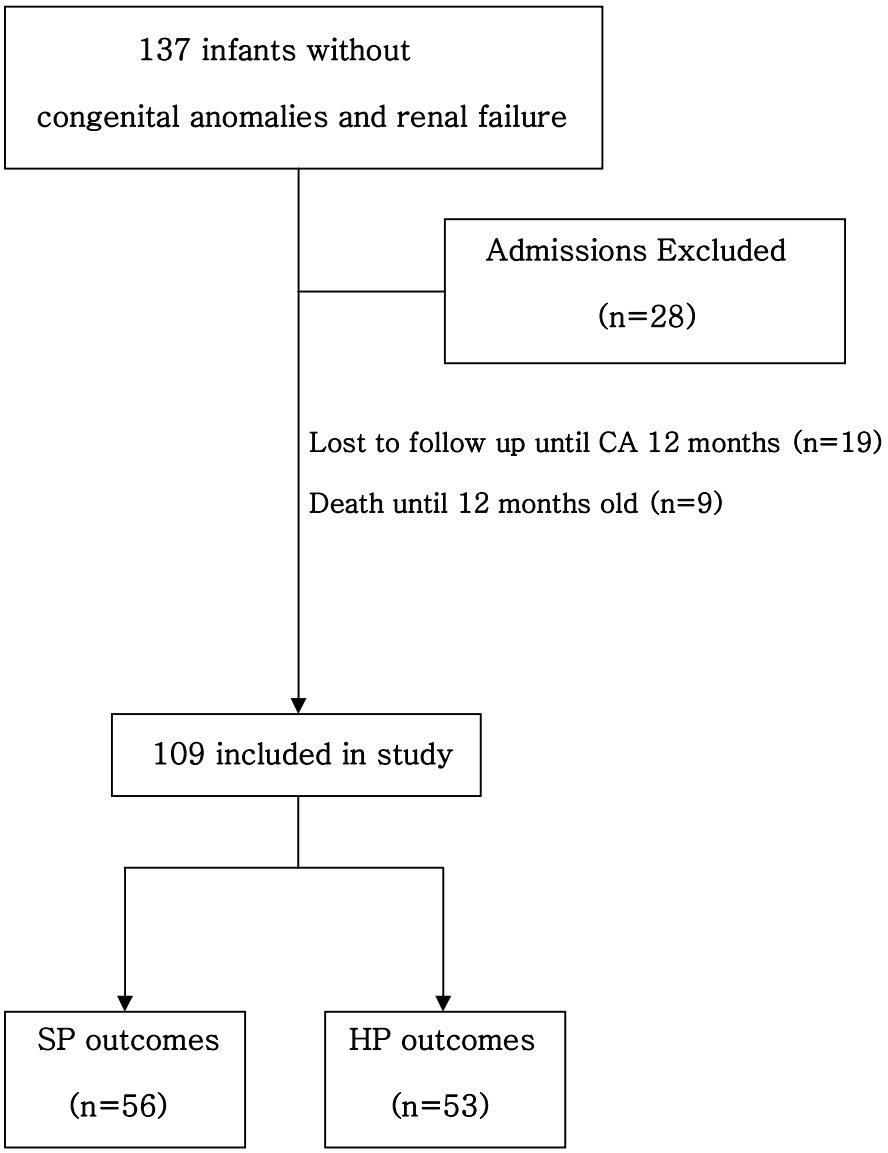
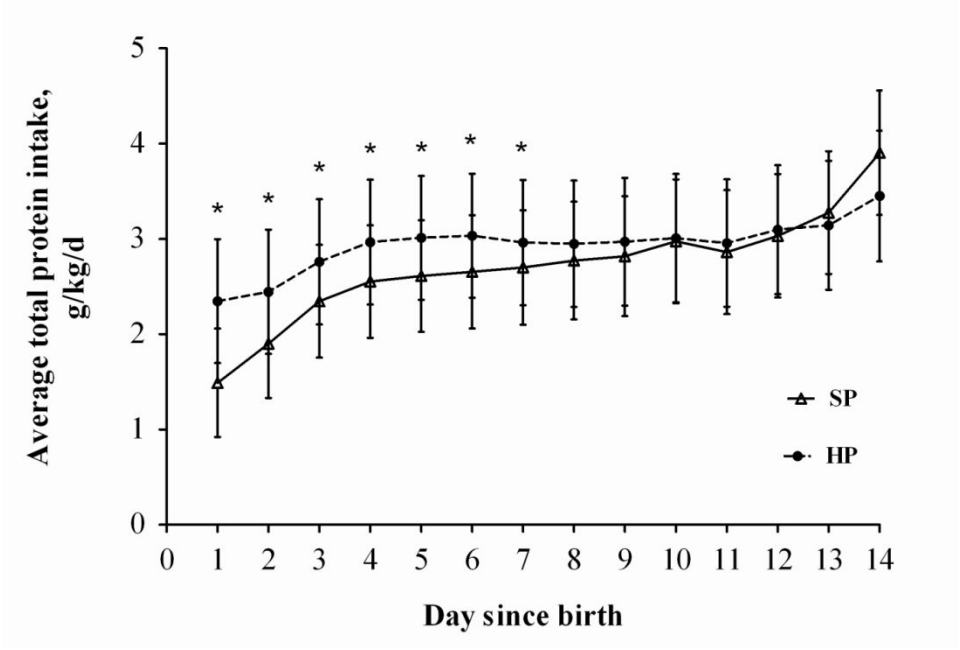
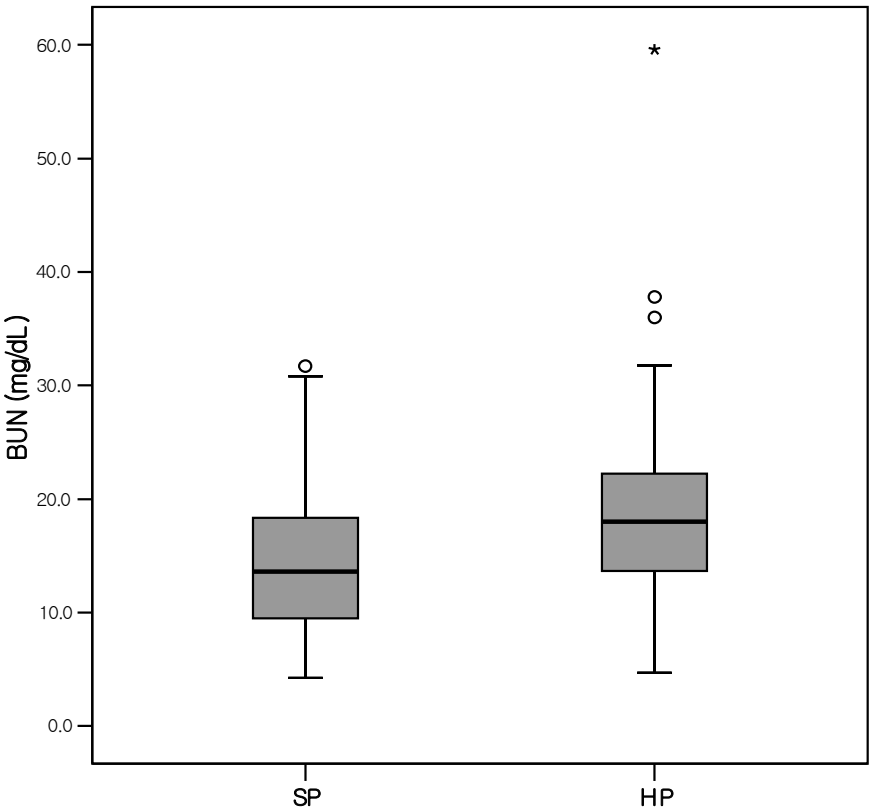


Figure 3. Mean ± SD value of the daily amino acid doses in patients managed with the standard protein (SP) and the high protein (HP) protocol (See text)



*$P < 0.05$

Figure 4. A comparison of mean blood urea nitrogen(BUN) level for two groups



Box and whiskers plot of maximum glucose level; Bars represent median, boxes and whiskers represent interquartile range and range, respectively. (p<0.05)

Figure 5. Correlation of mean amino acid dose with mean serum glucose level during the first 3 days of life

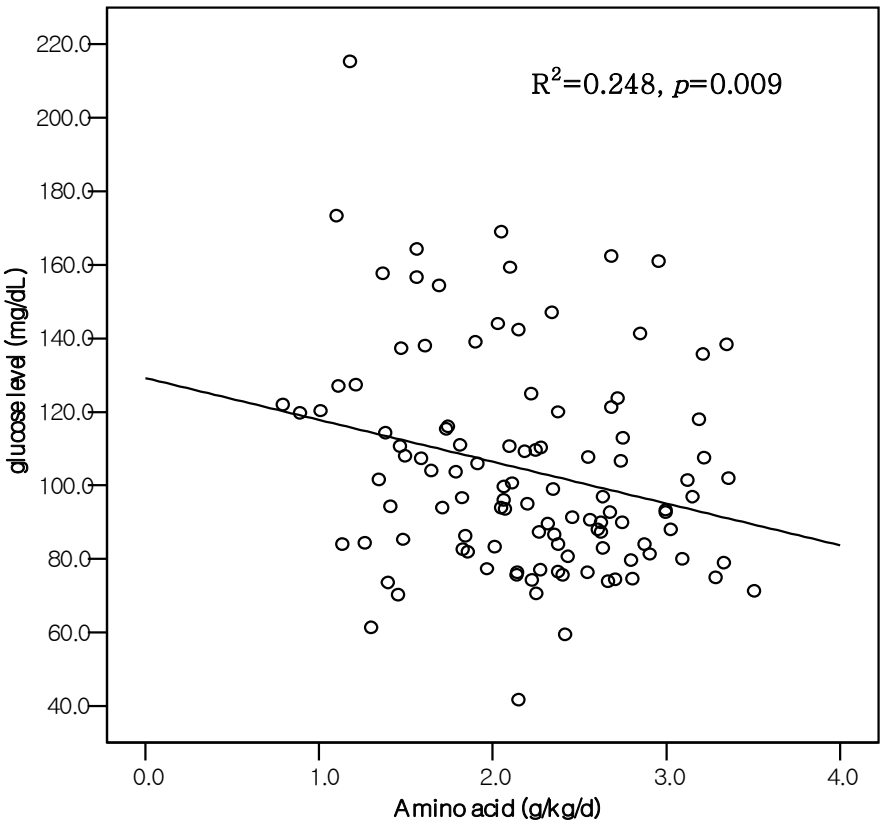
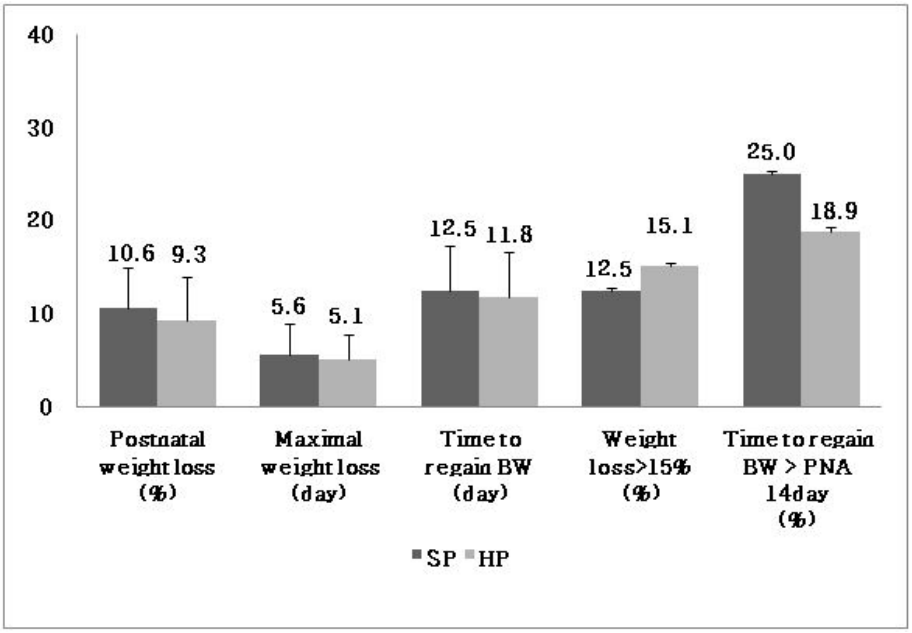


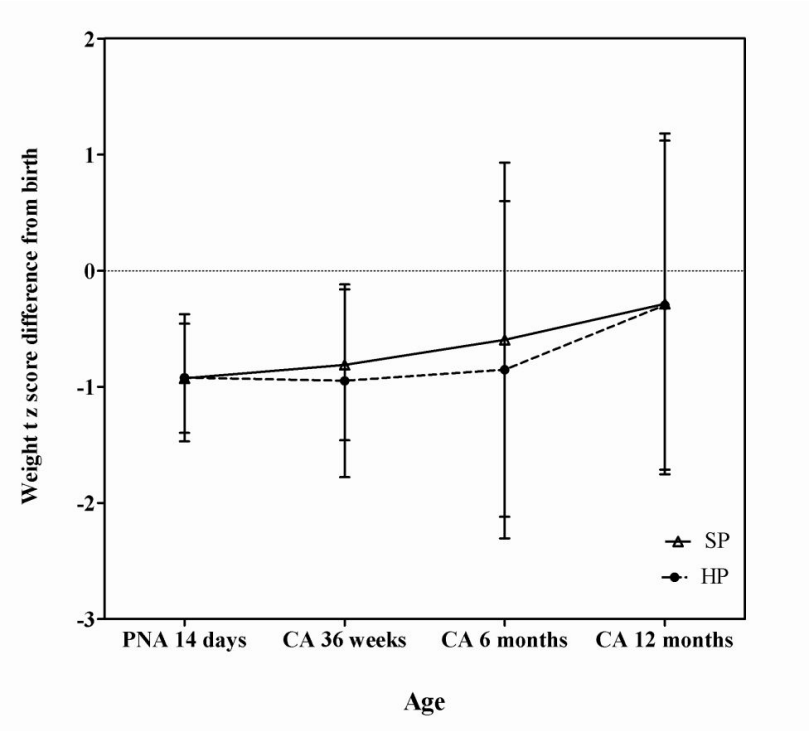
Figure 6. Body weight changes within two weeks of life



Continuous variables are presented as Mean + SD; Wt, indicates Weight; PNA, indicates postnatal age. Differences of all variables were statistically nonsignificant between two groups.

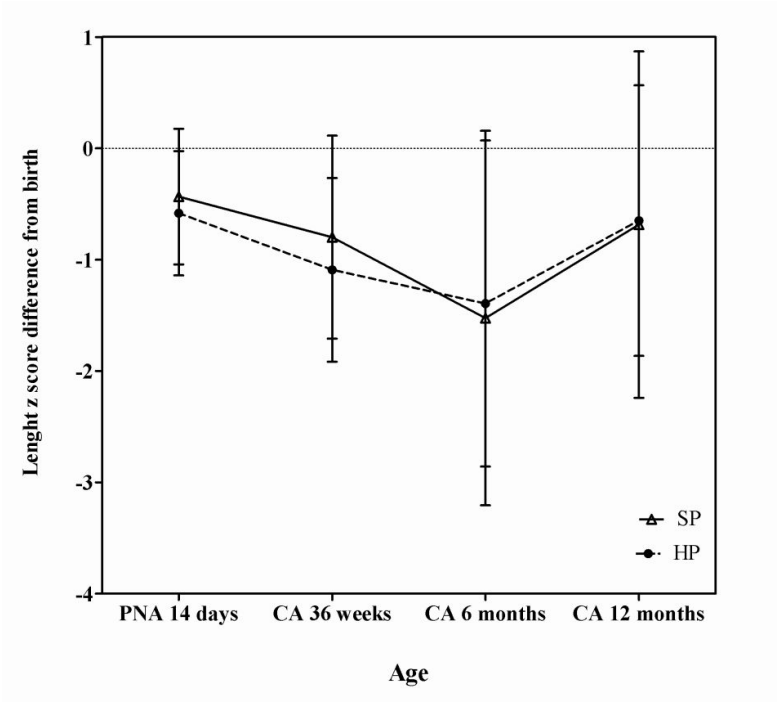
Figure 7. Z score change of growth parameters from birth to postnatal 14 days and 36 weeks, 6 months, and 12 months of corrected age: (A) weight, (B) height, and (C) Head circumference. Data are presented as mean ± SD

(A)



(continued)

(B)


Lenght z score difference from birth
1
0
-1
-2
-3
-4
SP
HP
PNA 14 days
CA 36 weeks
CA 6 months
CA 12 months
Age

(C)

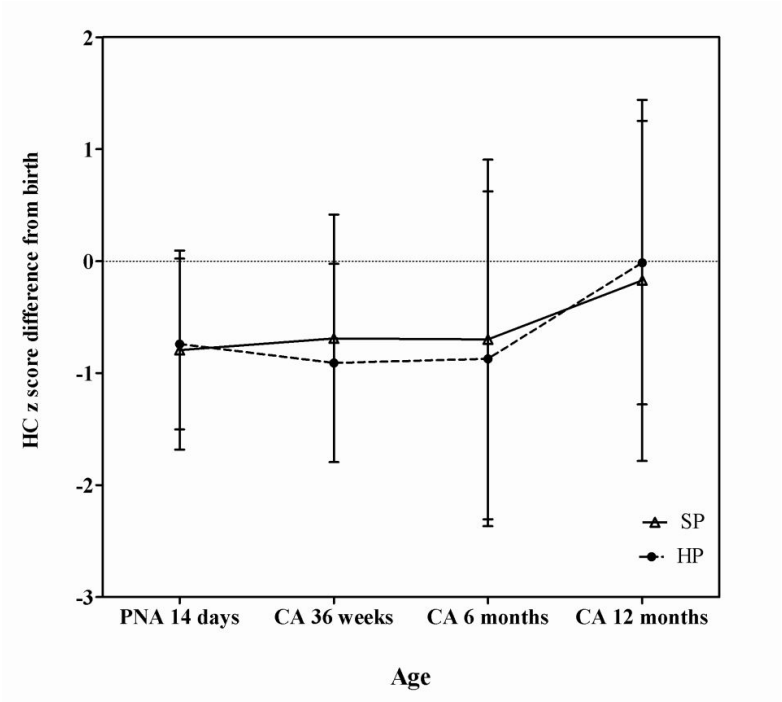

HC z score difference from birth
2
1
0
-1
-2
-3
SP
HP
PNA 14 days
CA 36 weeks
CA 6 months
CA 12 months
Age

Table 1. Evidence-Based Early Nutritional Practice for VLBW Infants: Recommendations and Evidence Quality

(Data are from reference 38)

Practice	Strength of Recommendation*	Evidence Quality†
Prompt provision of energy:		
Glucose infusion providing about 6 mg/kg/min Increase to about 10 mg/kg/d by 7 days of age Maintain blood sugar 50 -120 mg/dL	Recommended	B
Prompt provision of parenteral amino acids:		
Initiate 3.0 g/kg/d within hours of birth Advance to 4.0 g/kg/d by 0.5-1.0 g/kg/d steps	Recommended	B
Initiate lipid emulsion within the first 24-30 hrs of birth:		
Start 0.5 to 1.0 g/kg/d Advance to 3.0-3.5 g/kg/d by 0.5-1.0 g/kg/d steps	Recommended	B
Initiate trophic feedings by 5 days of age		
Provide about 10 mL/kg/ Begin advancing to 150 mL/kg/d by 10-20 mL/kg/d steps within the next several days	Recommended	B

*Strength of Recommendation: strongly recommended; recommended; option; not recommended.

†Grade of Evidence Quality: A, Well-designed, RCTs performed on appropriate populations; B, RCTs with minor limitations, overwhelmingly consistent evidence from observational studies; C, Observational studies (case-control and cohort design); D, Expert opinion (case reports, reasoning from first principles).

Table 2. Parenteral nutrition dosing strategies within 14 days of life

	Standard protein (SP)	High protein (HP)
Amino acid (g/kg/day)	Starting dose 1.5 Advancement: 0.5−1.0 Goal : 3.5−4.0	Starting dose 3.0
Dextrose (mg/kg/min)	Initiation : 4−8 Advancement : 1−3 Maximum 12−14	
Lipid (g/kg/day)	Initiation : 0.5−1 Advancement : 0.5−1 Goal : 3	
Isocaloric (kcal/kg/day)	Goal : 90−120	

Table 3. Demographic & Clinical characteristics of the study population

	SP (N=56)	HP (N=53)	*P* value
Gestational age(weeks) [a]	30.3 ± 2.3	30.1 ± 2.6	0.603
Birth weight (g)	1192 ± 232	1163 ± 240	0.520
Birth length (cm)	37.6 ± 2.7	37.9 ± 3.2	0.580
Birth HC(cm)	27.0 ± 2.0	26.6 ± 1.8	0.317
SGA, n(%)	19 (33.9)	14 (26.4)	0.413
Gender, Male : Female	29:27	23:30	0.391
Antenatal steroids, n(%)	42 (75.0)	34 (64.2)	0.297
Apgar score 1minute	5.6 ± 1.8	5.4 ± 2.0	0.632
Apgar score 5 minutes	7.6 ± 1.1	7.5 ± 1.5	0.691
CRIB II scores	6.4 ± 2.6	6.7 ± 3.2	0.576
Surfactant therapy, n(%)	9 (16.1)	14 (26.4)	0.242

[a] Data are presented as number (%) and mean ± SD unless otherwise specified.

HC, indicated Head Circumference; SGA, indicates Small for Gestational Age; CRIB, indicates Clinical Risk Index for Babies.

Table 4. Nutritional intake during the initial 14 days of life

	SP (N=56)	HP (N=53)	*P* value
Parenteral nutrition (day) [a]	32.2 ± 18.3	30.8 ± 20.3	0.925
Age at start enteral feeding (day)	3.4 ± 3.9	4.1 ± 5.6	0.790
Age at 130mL/kg (day)	11.1 ± 6.7	12.9±10.1	0.259
Fluid intake (mL/kg/d)	105.3 ± 12.6	104.6 ± 12.6	0.758
Enteral intake (mL/kg/d)	25.6 ± 23.6	26.8 ± 24.3	0.498
Total protein intake (g/kg/d)	2.6 ± 0.4	2.9 ± 0.4	<0.001
IV protein intake(g/kg/d)	2.2 ± 0.6	2.4 ± 0.5	0.010
Enteral protein intake (g/kg/d)	0.5 ± 0.5	0.5 ± 0.5	0.847
Nonprotein calories (kcal/kg/d)	72.5 ± 13.2	73.6 ± 10.9	0.618
BM+PM : PM : BM (n) [b]	43 : 10 : 3	38 : 13 : 2	0.549

[a] Data are presented as number (%) and mean ± SD unless otherwise specified.

IV, indicates intravenous; BM, indicates breast milk; PM, indicates premature milk.

Table 5. Nutrition-associated laboratory values during the initial 14 days of life

	SP (N=56)	HP (N=53)	P value
BUN (mg/dL) [a]	14.8 ± 6.7	19.2 ± 7.0	0.005
Peak BUN > 40 mg/dL, n (%)	5 (8.9)	9 (17.0)	0.259
Serum creatinine (mg/dL)	0.81 ± 0.19	0.79 ± 0.17	0.568
Bicarbonate (mEq/dL)	22.8 ± 2.3	22.4 ± 2.4	0.349
Base deficit	-2.9 ± 1.7	-3.6 ± 2.4	0.077
Serum glucose (mg/dL)	103.1 ± 23.3	105.7 ± 24.9	0.565
Serum glucose > 200mg/dL, n (%)	7 (12.5)	6 (11.5)	1.000
Serum K^+ (mg/dL)	4.2 ± 0.3	4.1 ± 0.3	0.123

[a] Data are presented as number (%) and mean ± SD unless otherwise specified.

BUN, indicates blood urea nitrogen; BST, indicates blood sugar test; PNA, indicates postnatal age.

Table 6. Neonatal morbidities between the HP and the SP groups at discharge

	SP (N=56)	HP (N=53)	P value
Oxygen therapy (day) [a]	12.3 ± 22.5	18.9 ± 27.1	0.167
Mechanical ventilation (day)	5.8 ± 11.7	9.5 ± 14.7	0.141
CA at discharge (week)	38.2 ± 2.4	37.6 ± 1.8	0.457
Length of stay (day)	54.9 ± 20.6	54.5 ± 21.6	0.925
BPD, n (%) [b]	11 (19.6)	15(28.3)	0.370
PDA, n (%)	22 (39.3)	27 (50.9)	0.251
PDA – surgery, n (%)	2 (3.6)	4 (7.5)	0.429
Early onset sepsis, n (%)	2 (3.6)	0 (0)	0.496
Late onset sepsis, n (%)	8 (14.3)	16 (30.2)	0.064
IVH ≥ grade 3, n(%)	1 (1.8)	0 (0)	1.000
ROP – surgery, n (%)	1 (1.8)	5 (9.4)	0.107
NEC/SIP, n (%)	0 (0)	0 (0)	–
Direct bilirubin > 2 mg/dL, n (%)	3 (5.4)	5 (9.4)	0.481

[a] Data are presented as number (%) and mean ± SD unless otherwise specified.

CA, indicates corrected age; BPD, indicates bronchopulmonary dysplasia; PDA, indicates patent ductus arteriosus; IVH, indicates intraventricular hemorrhage; ROP, indicates retinopathy of prematurity; NEC, indicates necrotizing enterocolitis; SIP, indicates spontaneous intestinal perforation.

Table 7. Multiple regression: adjusted independent variables determining z score between birth and 36 weeks of corrected age (CA)

	⊿ z score weight	⊿ z score length	⊿ z score HC
Gestational age[a]	−0.134 ± 0.050**	−0.175 ± 0.053**	−0.240 ± 0.054**
z score at birth	−0.466 ± 0.056**	−0.567 ± 0.061**	−0.708 ± 0.069**
CRIB II score	−0.045 ± 0.028	−0.071 ± 0.035*	−0.016 ± 0.162
Protein intake during 14d	0.038 ± 0.116	0.113 ± 0.154	0.025 ± 0.162
Hospitalization days	−0.018 ± 0.003**	−0.014 ± 0.005**	−0.020 ± 0.005**
Mean NPC during 14d	−0.001 ± 0.004	0.004 ± 0.006	0.006 ± 0.006
Goodness of fit (r^2)	0.691	0.575	0.633

[a]Data are presented as mean ± SD; HC, indicates head circumference; CRIB, indicates Clinical Risk Index for Babies; NPC, indicates nonprotein calorie.

* $P < 0.01$

** $P < 0.05$

국문초록

출생체중 1.5kg 미만의 극소 저 체중 미숙아에서 생후 첫 2주 간 아미노산 공급량에 따른 성장 및 대사상태 비교

서울대학교 보건대학원

보건학과 보건통계학전공

양 사 미

연구목적: 출생체중 1.5 kg 미만의 극소 저체중 미숙아는 위장기관이 구조적, 기능적으로 미성숙하여 정맥영양에 대한 의존도가 높다. 특히, 자궁 내 태아가 모체로부터 다량으로 공급받는 아미노산은 체내 단백 합성 및 중요한 열량 공급원으로 사용될 뿐 아니라, 생후 초기 고혈당증을 방지하는 데 효과가 있다고 알려져 있어 미숙아의 정상적 성장 및 발달을 위해서는 출생 초기에 적절한 양의 아미노산 투여가 필수적이다. 이에 본 연구에서는 출생체중 1.5kg 미만인 극소 저체중 미숙아에서 출생 초기 단백질

투여 용량 차이가 단기간, 장기간 성장 및 대사상태에 미치는 영향을 분석하고자 한다.

연구대상 및 방법: 2008 년 1 월부터 2009 년 12 월까지 서울아산병원 신생아중환자실에 입원한 출생체중 1.5kg 미만의 극소 저체중 미숙아를 대상으로 전자의무기록 조사를 통한 후향적 연구 분석을 하였다. 2008 년에 출생한 환자군 (표준단백투여군, SP)은 생후 첫 날 단백공급 목표량을 1.5g/kg/d 로 시작하여 하루 0.5g/kg/d 씩 증량해 최종 투여량을 3.5-4g/kg/d 에 이르도록 하였고, 2009 년 이후 출생한 미숙아(고용량단백투여군, HP)는 생후 첫 날 공급 목표량을 2 배로 증가시킨 3.0g/kg/d 로 시작하며, SP 군과 동일하게 하루 0.5g/kg/d 씩 증량하여 최종 공급량이 3.5-4g/kg/d 가 되도록 하였다. 두 그룹 간 성장 비교를 위해 생후 체중 변화, 출생체중 회복기간, 성장 변화량, 출생 시 신체계측치의 z score 와 생후 14 일 째, 교정연령 36 주, 생후 6 개월 및 12 개월 째 신체계측치의 z score 차이를 비교분석 하였다. 또한 BUN, 혈중 중탄산농도, 혈당, 혈중칼륨수치 등 아미노산 투여량과 관련된 혈액학적 수치와, 성장 발달에 영향을 줄 수 있는 비영양적 요인 및 합병증을 조사하였다.

연구결과: 109 명의 환자를 대상으로 분석한 결과, 생후 14 일 간 아미노산은 HP 군이 SP 군보다 11% 정도 많은 양이 투여되었다(2.9±0.4 vs 2.6±0.4 g/kg/d, p<0.001). 생후 첫 3 일 간 최고혈장포도당수치(peak plasma glucose level)는 HP 군이 SP 군 보다 유의하게 낮았으며(116±24 vs. 137±39 mg/Dl,

p<0.01), 14 일 간 평균 BUN(blood urea nitrogen) 수치는 HP 그룹이 SP 그룹보다 높게 측정되었다(19.2±7.0 vs 14.8±6.7 mg/dL, p<0.01). 출생으로부터 생후 14 일째, 교정연령 36 주, 6 개월, 12 개월 째 z score 의 변화량은 두 군 간에 유의한 차이가 없었으며, 다변량 회귀분석에서는 재태연령, 출생 시 신체계측치의 z score, 재원기간(p<0.05)이 출생으로부터 교정연령 36 주까지의 z score 변화량과 통계적으로 유의한 변수로 측정되어 미숙아의 성장에 독립적 예측인자로 의미가 있었던 반면, 아미노산 투여량과 성장속도 간에는 유의한 상관성을 보이지 않았다.

결론: 생후 14일 간 초극소 저체중 미숙아에게 투여하는 고 용량 아미노산은 표준 용량에 비하여 특별한 대사적 부작용 없이 출생 초기의 고혈당증 빈도를 감소시키는 데 유의한 변수로 작용하였다. 그러나 초극소 미숙아에서 출생 초기 아미노산 투여량과 출생 후 1년 간 성장 발달 간에는 뚜렷한 양-반응 관계를 보이지 않았다. 향후 전향적 연구를 통해 미숙아의 생후초기 고 용량 아미노산 투여에 따른 장기적 성장 평가 및 비용-효율성 분석이 필요할 것으로 생각된다.

Key words: 아미노산, 미숙아, 성장, 중환자 치료, 정맥영양

Student number: 2010-22103