# Influence of aggressive nutritional support on growth and development of very low birth weight infants

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**Summary**

*Aim:* To investigate the influence of the early postnatal aggressive nutritional support on the very low birth weight infants (VLBWI) during hospitalization. *Materials and Methods:* Surviving premature infants without obvious deformity, with gestational age more than 28 weeks and less than 32 weeks, birth weight 1,000 g to 1,500 g, admitted in NICU in Affiliated Children's Hospital of Suzhou University during 12 hours after birth and stay for two weeks or more from January 2008 to December 2011 were selected, including 44 cases (admitted from September 2010 to December 2011) in the observation group and 36 cases in the control group (admitted from January 2008 and September 2010). The infants in the observation group were treated by aggressive nutritional management, while traditional nutritional management for infants in the control group. The variations of nutritional intake, weight gain, jaundice index, blood biochemistry, serum electrolytes indexes, and complications were compared between the two groups. *Results:* Compared to the control group, the average growth rate and the albumin (ALB) and prealbumin (PA) levels two week after birth and before leaving hospital of the infants in the observation group was significantly higher ($p < 0.05$), and the incidence of the extrauterine growth retardation was significantly decreasing ($p < 0.05$). However, the days of hyperbilirubinemia, highest value of the serum bilirubin, duration of jaundice, platelets after intravenous nutrition, liver function, blood lipid levels, blood glucose, blood PH, serum creatinine, urea nitrogen, and electrolytes of the first day and the seventh day after birth and the incidence of parenteral nutrition-associated cholestasis (PNAC) and necrotizing enterocolitis (NEC) between the two group had no difference ($p > 0.05$). *Conclusion:* The implementation of aggressive nutritional management on the with VLBWI was safe and effective.

*Key words:* Aggressive nutritional support; Very low birth weight infants; Enteral nutrition; Parenteral nutrition.

## Introduction

Currently, the global incidence of preterm infants is 9.6% [1], including 22.5% low birth weight infant (LBWI) [2]. With the gradual improvement of the perinatal medicine and neonatal intensive care treatment technology, the survival rate of the VLBWI and the super low birth weight infant increases year by year and reaches 66.6% - 84% [3-5]. Subsequently, the situation for growth deficiency of the postnatal VLBWI is becoming more common, and extrauterine growth retardation (EUGR) occurs in some VLBWI. According to the reported clinical and experimental data, EUGR has irreversible long-term effects on the neural development of the future and the final height [1, 6, 7], and increases the liability risk of the cardiovascular disease and metabolic syndrome in adult [8, 9]. Therefore, formulating rational nutritional support programs to promote the growth and development of the VLBWI has become the focus work of NICU. Many previous researches are about early nutritional support for preterm infants, but recent studies show that the growth rate of the VLBWI from birth to 18-24 months of the corrected age is related to the outcomes of the neural development [7], but how about the efficacy and safety issues of the aggressive enteral and parenteral nutritional support in the entire hospital stay? Thus, the clinical data of the VLBWI hospitalized from January 2008 to December 2011 were retrospectively analyzed to discuss the influence on the parenteral and enteral nutritional support of the VLBWI during hospital stay.

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Revised manuscript accepted for publication September 14, 2013

## Materials and Methods

*Study objects and grouping*

Forty-four VLBWI admitted in neonatal NICU of the Affiliated Children's Hospital of Suzhou University from September 2010 to December 2011 were taken as the observation group, including 25 males and 19 females with mean gestational age 30.32 ± 1.360 weeks, mean birth weight 1,275.45 ± 114.434 g. Thirty-six VLBWI admitted in neonatal NICU of the Affiliated Children's Hospital of Suzhou University from January 2008 to September, 2010 were taken as the control group, including 22 males and 14 females with mean gestational age 30.67 ± 1.512 weeks, mean birth weight 1,303.08 ± 165.004 g. There were no significant difference in the rate of the gender, infants under gestational age, asphyxia, neonatal respiratory distress syndrome, birth weight and gestational age ($p > 0.05$) (Table1). This study was conducted in accordance with the declaration of Helsinki. and with approval from the Ethics Committee of Soochow University Affiliated Children's Hospital. Written informed consent was obtained from all participants.

Inclusion criteria: (1) Premature infants with gestational age <32 weeks and ≥ 28 weeks, birth weight < 1,500 g and > 1,000 g; (2) admission time < 12 hours and hospital stay ≥ two weeks; (3) steady vital signs, no cyanoderma, no apnea, completely oral feeding when left hospital, and (4) with complete medical history and clinical data.

Exclusion criteria: (1) Infants with congenital metabolic diseases, severe congenital heart disease and gastrointestinal malformations, and (2) infants with hospital stay < two weeks, poor sucking when left hospital or unstable vital signs.

Clin. Exp. Obst. & Gyn. - ISSN: 0390-6663
XLI, n. 6, 2014
doi: 10.12891/ceog17512014

Table 1. — *Comparison of general data for VLBWI between the two groups when admitted*

| Groups | Cases | Male/female (cases) | Infants under gestational age (%) | Asphyxia (%) | Respiratory distress syndrome of infants (RDS) (%) | Average gestational | Birth weight (g) age (weeks) |
|---|---|---|---|---|---|---|---|
| Observation group | 44 | 25/19 | 12 | 13 | 12 | 30.32±1.360 | 1275.45±114.434 |
| Control group | 36 | 22/14 | 13 | 9 | 6 | 30.67±1.512 | 1303.08±165.004 |
| $\chi^2$ value | | 0.092 | 0.21 | 1.347 | 2.033 | - | - |
| t value | | - | - | - | - | -1.08 | -0.882 |
| P value | | 0.762 | 0.886 | 0.246 | 0.154 | 0.282 | 0.381 |

*Methods*

Retrospective controlled study was used to collect the situation of the selected objects such as births, enteral and parenteral nutrition, weight gain, blood biochemistry, and physical development.

Observation group: The VLBWI of the observation group was treated by early aggressive enteral and parenteral nutritional management as follows: (1) parenteral nutrition: all cases admitted to hospital within 24 hours were treated by intravenous nutrition. Composition of intravenous nutrition: glucose: initial amount was four to six mg/(kg.min), increased one to two mg/(kg.min) for each day if tolerated until reaching requisite amount, the maximum was up to 13-17 g/(kg.d). Amino acids: amino acids were given within four hours or at least within 12 hours after birth, the initial amount was 2.0 g/(kg.d), reached 4.0 g/(kg. d) at the velocity of 0.5 - 1.0 g/(kg.d). Fat milk: fat milk was given within 24 hours after birth, the initial amount was 0.5 - 1.0 g/(kg.d), reached 3.0 g/(kg.d) at the velocity of 0.5 - 1.0 g/(kg.d), and stopped intravenous nutrition when the enteral nutrition reached 100 k cal/(kg.d). Bilirubin values and liver function were regular monitored, the fat milk was stopped being given if the bilirubin value was too high or the liver function was impaired. (2) Enteral nutrition: shield water milk (energy: 81 k cal/100 ml, protein: 2.2 g/100 ml) was used. Usually, the minimal enteral feeding (MEF) was given the day after birth, or at least five days after birth for the infants with serious condition if tolerated, increased 10-20 ml/(kg.d) for each day, and transited to full enteral feeding as soon as possible. Feeding was stopped or just restricting to MEF if intolerance appeared during feeding. Feeding patterns: oral feeding firstly, or tube feeding (usually interval) if uncoordinated swallowing condition occurred in the infants or conditions did not allow oral feeding, then gradually transiting to oral feeding.

Control group: the VLBWI of the control group were treated by traditional nutritional management as follows: (1) parenteral nutrition: composition of intravenous nutrition: Glucose: initial amount was four to six mg/(kg.min), increased one to two mg/(kg.min) for each day if tolerated until reaching requisite amount, the maximum was up to 13 - 17 g/(kg.d). Amino acids: amino acids were given within 24-48 hours after birth, the initial amount was 0.5 g/(kg.d), reached 3.0 - 3.5 g/(kg.d) at the velocity of 0.5 g/(kg.d). Fat milk: fat milk was given three days after birth, the initial amount was 0.5 g/(kg.d), reached 3.0 g/(kg.d) at the velocity of 0.5 g/(kg.d). Bilirubin values and liver function were regular monitored, the fat milk was stopped to be given if the bilirubin value was too high or the liver function was impaired. (2) Enteral nutrition: shield water milk (energy: 81 k cal/100 ml, protein: 2.2 g/100ml) was used. Usually, the MEF was given five days after birth if tolerated, increasing 5-10 ml/(kg.d) for each day, and transiting to full enteral feeding as soon as possible. For infants with the assistance of breathing machine or CPAP machine, began MEF after removing the machines. Feeding patterns: oral feeding firstly, or tube feeding (usually interval feeding) if uncoordinated swallowing condition occurred in the infants or conditions did not allow oral feeding, then gradually transiting to oral feeding.

*Observing indexes*

(1) Observing and comparing the albumin (ALB) and prealbumin (PA) levels of the day, two weeks after birth, before leaving hospital, the time for regaining birth weight, the rate of gaining weight, the time of reaching full enteral feeding (PN time), neonatal necrotizing enterocolitis (NEC), parenteral nutrition associated cholestasis (PNAC) and the incidence of EUGR when left hospital. (2) Observing and comparing the days of hyperbilirubinemia occurring and duration of jaundice and the detection of platelet count (PLT) after parenteral nutrition (PN), the total cholesterol (TC), triglyceride (TG), alanine aminotransferase(ALT), and total bilirubin (TB). (3) Observing and comparing the values such as serum creatinine, urea nitrogen, pH, and electrolytes of the first day and the seventh day after birth.

*Related diagnostic criteria*

(1) Hyperbilirubinemia: The VLBWI or infants with other risk factors were more susceptible to bilirubin encephalopathy, and there was risk of bilirubin encephalopathy when the TB reached 171.0 - 205.2 μmol/l [10]. Therefore, the hyperbilirubinemia in this study was defined as > 171 μmol/l. (2) Days of hyperbilirubinemia: the days of the serum total bilirubin > 171 μmol/l. (3) Duration of jaundice: period between the start of yellow skin and the end of the jaundice vanishing. (4) PNAC: application time of parenteral nutrition ≥ two weeks, and serum direct bilirubin ≥ 25.6 μmol/l. (5) EUGR: the growth and development indexes were above or under the 10$^{th}$ percentile of the expected values for the corresponding intrauterine growth rate [11].

*Statistical analysis*

Data were analyzed using SPSS17.0 statistical software. Measurement data in line with normal values were indicated as ±s, the measurement data between the two groups were compared using t test, enumeration data between the two groups were compared using $\chi^2$ test, and $p < 0.05$ indicated that the differences had no statistical significance.

## Results

*Comparison of general data for VLBWI between the two groups when admitted*

There were no significant differences in the number of cases, gender, gestational age, birth weight, the incidence of infants under gestational age, and the fundamental disease between the two groups ($p > 0.05$, Table 1).

*Comparison of nutritional reserves and nutritional biochemical indexes between the two groups*

The differences of the time for regaining birth weight and the time for reaching full enteral feeding between the two

Table 2. — *Comparison of nutritional reserves and nutritional biochemical indexes between the two groups.*

| Groups | Cases | Velocity of gaining weight (g/kg.d) | Time for oral feeding (d) | Time for regaining birth weight (d) | Time for reaching full length intestine feeding (d) | The day after birth | | Two weeks after birth | | Leaving hospital | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ABL (mg/l) | PA (g/l) | ABL (mg/l) | PA (g/l) | ABL (mg/l) | PA (g/l) |
| Observation group | 44 | 21.80±2.952 | 2.14±1.391 | 8.23±5.794 | 27.73±11.050 | 32.30± 3.470 | 70.43± 18.918 | 34.55± 2.090 | 93.09± 18.632 | 35.45± 2.006 | 104.75± 34.644 |
| Control group | 36 | 17.74±4.862 | 6.67±3.347 | 11.22±6.076 | 31.17±14.962 | 32.27± 2.250 | 75.85± 21.376 | 30.79± 1.823 | 80± 20.296 | 31.72± 2.141 | 79.31± 23.402 |
| *p* value | | 0.000 | 0.000 | 0.027 | 0.241 | 0.996 | 0.233 | 0.000 | 0.004 | 0.000 | 0.000 |

Table 3. — *Comparison of the jaundice and the biochemical indices after PN between the two groups.*

| Groups | Cases | Days of hyperbilirubinemia occurring (d) | The highest value of serum bilirubin (mg/dl) | Duration of jaundice (d) | Ending of PN | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | PLT ($10^9$/ L) | CHOL (mmol/L) | TG (mmol/l) | ALT (u/l) |
| Observation group | 44 | 3.97±0.77 | 13.93±2.292 | 9.30±4.448 | 231.67±79.532 | 2.45±0.952 | 0.91±0.67 | 13.52±14.117 |
| Control group | 36 | 3.58±1.301 | 14.55±5.235 | 9.72±7.067 | 205.58±81.187 | 2.07±1.068 | 0.70±0.419 | 12.66±10.921 |
| *p* value | | 0.154 | 0.543 | 0.789 | 0.220 | 0.159 | 0.170 | 0.792 |

Table 4. — *Comparison of experimental indexes such as acid-base balance and electrolyte between the two groups.*

| Groups | Cases | pH | | BUN | | CR | | GLU | | Na | | K | | Cl | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | The first | The seventh | The first | The seventh | The first | The seventh | The first | The seventh | The first | The seventh | The first | The seventh | The first | The seventh |
| Observation group | 44 | 7.33± 0.18 | 7.35± 0.17 | 3.03± 2.348 | 4.78± 2.377 | 50.2± 13.0 | 66.5± 16.1 | 4.1± 1.4 | 5.4± 0.6 | 138.6± 7.5 | 140.3± 7.2 | 4.7± 1.1 | 5.1± 1.2 | 96.3± 6.3 | 97.4± 5.1 |
| Control group | 36 | 7.34± 0.17 | 7.360± 0.16 | 3.75± 3.253 | 4.35± 2.358 | 49.5± 12.9 | 66.9± 16.3 | 4.3± 1.2 | 5.2± 0.9 | 139.2± 7.8 | 140.8± 7.7 | 4.6± 1.0 | 5.0± 1.1 | 96.6± 6.7 | 97.3± 6.1 |
| *p* value | | 0.767 | 0.887 | 0.259 | 0.423 | 0.832 | 0.872 | 0.542 | 0.431 | 0.654 | 0.893 | 0.753 | 0.932 | 0.931 | 0.899 |

groups had no statistical significance ($p > 0.05$), but the time was shorter in the observation group than that in the control group. The rate of gaining weight in the observation group was obviously faster than that in the control group, the difference had statistical significance ($p < 0.05$). The differences of ABL and PA levels between the two groups when admitted had no statistical significance ($p > 0.05$), but the difference of ABL and PA levels in the observation group was obviously higher than that in the control group two weeks after birth and before leaving hospital, suggesting the difference had statistical significance ($p < 0.05$) (Table 2).

*Comparison of the jaundice and the biochemical indexes after PN between the two groups*

There were no significant differences in the days of hyperbilirubinemia occurring, the highest value of serum bilirubin and the duration of jaundice between the two groups ($p > 0.05$). The differences of the PLT after PN, the liver function and the blood lipid levels between the two groups had no statistical significance ($p > 0.05$, Table 3).

*Comparison of experimental indexes such as acid-base balance and electrolyte between the two groups*

The differences of blood glucose, PH, serum creatinine, urea nitrogen, and electrolyte levels on the first day and the seventh day after birth had no statistical significance ($p > 0.05$, Table 4).

*Comparison of hospital stay and complications between the two groups*

There were no significant differences in the PNAC, the NEC, and the incidence of sepsis during hospitalization rate between the two groups ($p > 0.05$), but incidence of the observation group was lower than that of the control group, and the time of the hospital stay for the observation group was significantly shorter than that for the control group ($p < 0.05$). The incidence of EUGR in the observation group was significantly lower compared with that in the control group, suggesting significant differences ($p < 0.05$, Table 5).

## Discussion

EUGR was a major problem for worldwide VLBWI. Preterm infants had to go through the process of catch-up growth after birth, but the time was very short. The most rapid speed for catching up was three months after birth, and the critical growing period for head circumference was only the first year after birth. If there was no catch-up growth in the critical period, the chance for later was very limited so that the neural development and the final

Table 5. — *Comparison of hospital stay and complications between the two groups.*

| Groups | Cases | Hospital stay (days) | EUGR n (%) | PNAC n (%) | NEC n (%) | Septicemia n (%) |
|---|---|---|---|---|---|---|
| Observation group | 44 | 43.93±9.978 | 19 (43.2) | 4 (9.1) | 3 (6.8) | 2 (4.5) |
| Control group | 36 | 51.03±16.636 | 27 (75) | 6 (16.7) | 4 (11.1) | 3 (8.5) |
| $\chi^2$ value | | - | 8.203 | 1.03 | 0.457 | 0.485 |
| t value | | 2.36 | - | - | - | - |
| *p* value | | 0.021 | 0.004 | 0.308 | 0.499 | 0.486 |

height were irreversibly affected in the future [1, 6, 7]. It was reported that the nutritional deficiency of the VLBWI and the low birth weight children after birth could be reduced due to the early aggressive nutrition support (including enteral and parenteral nutrition) [12]. Giving nutritional support with high energy and high protein for the VLBWI could reduce the incidence of EUGR [13, 14], and the safety of high-protein nutritional support in the early days after birth was explicit [15, 16]. Therefore, the early aggressive enteral and parenteral nutrition support were advocated both at home and abroad to promote the early postnatal catch-up growth and reduce the incidence of EUGR [17]. The results of the retrospectively analysis for the clinical data of the VLBWI treated by aggressive nutrition support in the entire hospital stay showed that the growth rate of the average weight for the observation group was significantly shorter than that for the control group, but the hospital stay was longer. Although the time of regaining birth weight and the time of reaching full length-intestine nutrition in the observation group were shorter than that in the control group, but the difference had no statistical significance. Inconsistent with the report in the foreign literature which confirmed the aggressive nutritional management could shorten the time to regain birth weight [18], the results in this study might be related to the less than normal number of cases, so further in-depth study should be performed in the future. Serum ABL with half-life of 25-26 days and serum PA with half-life of only 1.9 days were mainly synthesized by the liver. The changes of the ALB and PA due to the changes of protein and energy in vivo would provide evaluated indicators for nutritional reserves of the premature infants. It was generally believed that the early postnatal nutritional status could be reflected by the values of the first two weeks after birth, and the values before leaving hospital reflected the overall nutritional status during hospitalization [19]. The results in this study showed that the ABL and PA levels of the observation group two weeks after birth and before leaving hospital were significantly higher compared with that of the control group, indicating that the aggressive nutritional management could significantly increase the body's nutritional reserves of the VLBWI. The incidence of EUGR in the observation group was significantly decreased, indicating that aggressive nutritional management could promote early growth and development of the VLBWI and reduce the incidence of EUGR. This nutritional management was effective, but how about its security?

It was known that the natural energy reserves of the VLBWI were limited. According to Heird [20], the VLBWI could only survive for four days only depended on their natural energy reserves without absorbing exogenous energy. Certainly, the quick intake of the carbohydrate could be used to replenish the lost energy, but this would lead to negative nitrogen balance and self-protein deficiency of the VLBWI, which happened in the early stage would affected their neural development of the VLBWI. At least 1.5 g/kg of proteins were given daily in order to achieve a positive nitrogen balance. Therefore, the current domestic and international research recommended amino acid giving within a few hours after birth, the initial amount was 2.0 g/(kg.d), gradually reaching 0.5 - 1.0 g/(kg.d) at a velocity of 4.0 g/(kg.d). However due to the early studies suggested that high doses of amino acids to VLBWI could cause metabolic acidosis, renal dysfunction, and other diseases [21], many clinicians currently still followed the traditional nutrition policies. In this study, compared with the control group, the early postnatal supply of amino acids did not increase metabolic acidosis, renal dysfunction, electrolyte imbalance, and other disease in the observation group, which was in line with the study of Thureen *et al.* [22], indicating that the application of early aggressive clinical amino acid was safe.

The early postnatal enteral nutrition of the VLBWI could not meet their caloric needs, therefore the supply of the energy mainly relies on fat milk. Although the optimal amount fat intake constituted for body organization remained unclear, research institutions at home and abroad all recommended to begin giving fat milk within 24 hours after birth, the initial amount was 0.5 - 1.0 g/(kg.d), and reaching 3.0 g/(kg.d) at the velocity of 0.5-1.0 g/(kg.d). However, since the systems of the preterm infants were immature, early application of adequate fat milk to preterm infants could aggravate neonatal jaundice, cause hyperlipidemia, cholestasis, liver damage, and other diseases [23]. In addition, the current clinical application of soy-derived fat milk was rich in n-6 fatty acids, which had proinflammatory mechanisms and could promote hepatic apoptosis and necrosis [23, 24], and arachidonic acid (one of the derivatives for n-6 fatty acids) could lead to dysfunction, adhesion reduction, and quantitative reduction of the platelet, which manifested bleeding in clinics [24]. Therefore, at present, many clinicians still tended to use the traditional nutrition programs, that is, beginning giving fat milk from the third day after birth, slowly increasing the dose and reaching a sufficient amount on the sixth day after birth. At least 0.5 $g.kg^{-1}.d^{-1}$fat milk was needed for preterm infants to prevent the essential fatty acid deficiency [25], but many clinicians often applied a higher dose fat milk to meet the need of infant growth. Long-term parenteral nutrition was not needed by most preterm infants in the NICU, so the minimum amount of fat milk strategy was not necessary for most infants [23, 26]. In this study, fat milk was given 24 hours after birth, but the days of hyperbilirubinemia occurring, the highest value of serum bilirubin, the duration of jaundice, and the PLT, liver function, serum lipids, incidence of PNAC after PN of the observation group had no significantly increasing compared with that of the control group. Visibly, early application of fat milk did not increase the risk of bleeding, jaundice, liver dysfunction, and cholestasis in the VLBWI, which was consistent with the findings of Ibrahim *et al.* [27], indicating that the aggressive application of fat milk nutrition during hospitalization for the VLBWI was safe.

It was conventionally believed that too early initiation of enteral nutrition could lead to an increased incidence of NEC, therefore, more clinicians currently tended to commence intestinal feeding rather later. However, studies showed that early initiation of enteral feeding, such as beginning receiving parenteral MEF five days after birth did not increase the incidence of NEC [28, 29]. In this study, the average time for starting milk feeding was 2.14 days after birth for the observation group, and 6.67 days for the control group; the incidence of NEC between the groups had no significant differences, indicating that accepting intestinal feeding after birth for the VLBWI did not increase the incidence of NEC.

This study suggested that giving aggressive vein and intestinal feeding for the VLBWI during hospitalization was safe and effective, which deserved more clinicians promoting and researching in order to better promote the growth and development of the VLBWI and improve long-term prognosis. The present also need follow-up studies for further long-term neural development.

## Acknowledgements

This study was supported by the Science and Technology Development Project of Suzhou (No.: SYS201136); the Research Project of Jiangsu Province Health Department (No.: H201316), Research Project of the Suzhou Key Laboratory of Children's Developmental Brain Injury Prevention and Care (No. SZS201108).

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