An aggressive parenteral nutrition protocol improves growth in preterm infants

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Received: 22 December 2014, Revised: 27 May 2015, Accepted: 29 July 2015

SUMMARY: Törer B, Hanta D, Özdemir Z, Çetinkaya B, Gülcan H. An aggressive parenteral nutrition protocol improves growth in preterm infants. Turk J Pediatr 2015; 57: 236-241.

The objective of this study was to compare postnatal growth and clinical outcomes of preterm infants after an adjustment in amino acid and lipid administration practice. The study was conducted retrospectively in preterm infants with a birth weight < 1250 g for the periods January–June 2007 and June–November 2010. In 2007, amino acid solution was initiated at 2 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 3 g/kg/day; lipid solution was initiated at 1 g/kg/day on the first day of life and advanced 0.5 g/kg/day to a maximum of 2 g/kg/day (low-dose parenteral nutrition group). In 2010, amino acid solution was initiated at 3 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 4 g/kg/day; lipid solution was initiated at 1 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 3 g/kg/day (high-dose parenteral nutrition group). Patient characteristics were similar in the two groups. Infants in the high-dose parenteral nutrition group showed a significant reduction in the time needed to regain birth weight and a significant reduction in the maximum weight loss. Weight, length and head circumference at discharge were significantly higher in the high-dose parenteral nutrition group. The mean duration of parenteral nutrition, mean number of days to reach full enteral feeding and incidence of sepsis and necrotizing enterocolitis were significantly lower in the high-dose parenteral nutrition group. There was no significant difference in the mortality rate between the groups. In conclusion, a more aggressive parenteral nutrition protocol for preterm infants resulted in a more rapid increase in weight, length and head circumference, and decreased incidence of sepsis and necrotizing enterocolitis.

Key words: premature, parenteral nutrition, postnatal growth, clinical outcomes.

Early protein and energy intake in the first week of life is crucial for preterm infants. Nutritional deficits in this critical period are rarely compensated for and usually contribute to subsequent postnatal growth restriction and poor long-term outcomes[1-4]. Despite improved knowledge concerning early nutrition for preterm infants, nutritional practices continue to vary among neonatal intensive care units[5]. There is controversy regarding the timing of initiation of parenteral nutrition, the amount of the initial dose, the advancement of the dosages, and the maximal dosages of amino acids and lipids.

Our nursery policy has been to initiate amino acid and lipid solutions on the first day of life. However, low initial doses were chosen to avoid metabolic complications. In 2010, our policy changed to favor higher initial doses, and faster advancement of amino acid and lipid dosages with higher maximal target doses.

This study was designed to compare the postnatal growth and clinical outcomes of preterm infants during two different periods of time, i.e., before and after modification of our nutritional protocol.

Material and Methods

The study was conducted retrospectively in the Neonatal Intensive Care Unit of Baskent

University Hospital for the periods January-June 2007 and June-November 2010. Preterm infants with a birth weight < 1250 g were included in the study. Infants with major congenital anomalies and infants transferred from other hospitals after the first 24 hours of life were excluded. In 2007, amino acid solution (Primene, Eczacıbası, Baxter, Turkey) was started at 2 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 3 g/kg/day; lipid solution (20% lipid solution, Intralipids, Eczacıbası, Baxter, Turkey) was started at 1 g/kg/day on the first day of life and advanced 0.5 g/kg/day to a maximum of 2 g/kg/day (low-dose parenteral nutrition group: LDPN group). In 2009, we revised our nutritional protocol based on recent recommendations. In 2010, amino acid solution (Primene, Eczacıbası, Baxter, Turkey) was started at 3 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 4 g/kg/day; lipid solution (20% lipid solution, Intralipids, Eczacıbası, Baxter, Turkey) was started at 1 g/kg/day on the first day of life and advanced 1 g/kg/day to a maximum of 3 g/kg/day (high-dose parenteral nutrition group: HDPN group). Administration of fluids, glucose, electrolytes and vitamins were unchanged with the new protocol. Glucose infusion was initiated at 4-6 mg/kg/min and increased by 2 mg/kg/min to a maximum of 10 mg/kg/min. Enteral feeding was started within the first day at 10 ml/kg/day in both groups and advanced by 10-20 ml/kg/day to full enteral nutrition. As the feedings were advanced, IV fluids were decreased proportionately. Each infant's weight was measured daily, and length and occipital-frontal head circumference weekly until discharge. Perinatal data (gestational age, gender, birth weight, growth restriction at birth and use of antenatal steroids), growth and anthropometric measurements, biochemical parameters and clinical conditions (respiratory distress syndrome, sepsis, patent ductus arteriosus, intracranial hemorrhage grade 3-4, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, cholestasis, length of hospital stay and mortality) were assessed at discharge or at death.

Statistical analyses were performed with SPSS 11 for Windows. A chi-square test was used for categorical variables. Student's *t*-test and its nonparametric counterpart, the Mann–Whitney *U* test, were used for continuous variables.

Results

A total of 96 infants (58 females and 38 males) were analyzed. The mean birth weight was 1015.11±157.2 and the mean gestational age was 28.62±2.26 weeks. There were 45 infants in the LDPN group and 51 in the HDPN group. Patient characteristics in both groups were similar but the proportion of infants who had received antenatal steroids was higher in the HDPN group (Table I). A comparison of growth and anthropometric measurements is presented in Table II. The maximum postnatal weight loss was significantly higher in the LDPN group; the mean number of days to regain birth weight was significantly lower in the HDPN group. The mean duration of parenteral nutrition and the mean number of days to reach full enteral feeding were significantly lower in the HDPN group. By day 28, there were no significant differences between the groups of infants in weight, length or head circumference, but infants in the HDPN group displayed a significantly greater average daily weight gain. Growth parameters

Table I. Patient Characteristics

	LDPN group (n=45)	HDPN group (n=51)	p
Gestational age (weeks) mean ± SD	28.62 ± 2.02	28.80 ± 2.46	0.575
Birth weight (g) mean ±SD	1045.11 ± 157.20	988.63 ± 180.68	0.137
Birth length (cm) mean ± SD	36.06 ± 1.92	35.07 ± 3.04	0.082
Birth head circumference (cm) mean ± SD	25.05 ± 2.38	25.38 ± 1.84	0.654
Male gender, n (%)	17 (37.8%)	21 (41.2%)	0.448
Antenatal steroids, n (%)	14 (31.1%)	32 (62.7%)	0.002
Birth weight <10 percentile, n (%)	5 (11.1%)	13 (25.5%)	0.061

and growth rates were significantly greater in the HDPN group at discharge. Infants in the HDPN group displayed higher BUN levels on day 2 and less hypoglycemia and hypocalcemia (Table III). The incidences of sepsis and necrotizing enterocolitis were significantly lower in the HDPN group (Table IV). There was no significant difference between the groups in length of stay and mortality.

Discussion

The desirability of the early provision of parenteral amino acids and lipids to preterm infants is a concept supported by a number of studies[1, 6-28]. However, nature of the interventions, the composition of the parenteral nutrition, and the populations of preterm infants in these studies are heterogeneous. There is some degree of overlap in the timing of the initiation of parenteral nutrition between "early" and "late" groups. In this study, we compared the growth and clinical outcomes of preterm infants before and after modifying our parenteral nutrition protocol. For both groups, we initiated parenteral amino acid and lipid solutions on the first day of life, but infants in the HDPN group received higher doses of amino acid and lipid solutions (higher initial dose, more rapid enhancement and higher maximal dose). HDPN group infants required less time to regain birth weight and showed less postnatal weight loss. Previous studies support this finding[1, 7-8, 11-12, 15, 20-23, 27]. Moyses et al.[7] reported a meta-analysis evaluating the effect of early parenteral nutrition and showed less initial weight loss and time to regain birth weight as well as greater weight and length at discharge or 36-week postmenstrual age with early parenteral nutrition. In our study, in contrast to findings of other investigators, weight, length and head circumference at discharge were greater in the HDPN group[6, 8, 9, 14, 17, 20, 28]. Uthaya et al.[6] reviewed seven randomized controlled trials comparing low or incremental versus high intake of amino acids and found that the benefits of higher amino acid intake on short- and long-term growth were not established in these studies. However, the dosages of amino acids and lipids administered were different in the studies. As a result, the amount of energy provided was quite variable. The higher intake of amino acids combined with higher intake of lipids in the HDPN group is likely to have contributed to

Table II. Growth and Anthropometric Measurements

	LDPN group (n=45) (mean ± SD)	HDPN group (n=51) (mean ± SD)	p
Maximum postnatal weight loss (%)	11.89 ± 5.80	9.01 ± 5.36	0.027
Days to regain birth weight (days)	13.04 ± 5.00	9.67 ± 4.47	0.001
Duration of parenteral nutrition (days)	31.49 ± 20.25	19.35 ± 1.44	0.001
Days to reach full enteral nutrition	31.40 ± 15.14	20.57 ± 9.40	0.001
Weight on day 28 (g)	1371.36 ± 271.24	1404.90 ± 316.26	0.506
Length on day 28 (cm)	38.72 ± 2.41	38.63 ± 3.29	0.854
HC on day 28 (cm)	27.52 ± 2.14	28.01 ± 2.51	0.272
Weight gain as of day 28 (g/day)	11.39 ± 6.00	14.26 ± 6.20	0.013
Growth in length as of day 28 (cm/week)	0.65 ± 0.45	0.89 ±0.57	0.070
Growth in HC as of day 28 (cm/week)	0.61 ± 0.34	0.65 ± 0.40	0.403
Weight at discharge (g)	1836.89 ± 389.27	2150.59 ± 738.19	0.008
Length at discharge (cm)	41.39 ± 2.85	42.96 ± 3.90	0.017
HC at discharge	29.43 ± 1.86	31.42 ± 2.50	0.001
Weight gain at discharge (g/day)	16.56 ± 4.92	21.44 ± 5.18	0.001
Growth in length at discharge (cm/week)	0.11 ± 0.14	0.15 ± 0.07	0.001
Growth in HC at discharge (cm/week)	0.08 ± 0.03	0.12 ± 0.05	0.001

HC: Head circumference

Table III. Biochemical Parameters

	LDPN group (n=45)	HDPN group (n=51)	p
Serum BUN level on day 2 (mg/dl)	19.53 ± 9.19	24.12 ± 9.49	0.012
Serum creatinine level on day 2 (mg/dl)	0.81 ± 0.27	0.78 ± 0.20	0.632
Serum BUN level on day 7 (mg/dl)	26.36 ± 13.73	27.39 ± 14.08	0.686
Serum creatinine level on day 7 (mg/dl)	0.58 ± 0.19	0.61 ± 0.16	0.539
Serum triglyceride level on day 7 (mg/dl)	143.68 ± 92.85	116.00 ± 47.75	0.493
Hypoglycemia[1], n (%)	24 (53.3%)	15 (30.0%)	0.024
Hypocalcemia[2], n (%)	16 (35.6%)	8 (15.7%)	0.034
Hyperglycemia[3], n (%)	20 (44.4%)	23 (45.1%)	1.000
Metabolic acidosis[4] on day 3, n (%)	6 (13.3%)	11 (21.6%)	0.422
Metabolic acidosis[4] on day 7, n (%)	4 (8.9%)	4 (7.8%)	1.000

BUN: Blood urea nitrogen
[1]Hypoglycemia (serum glucose <50 mg/dl)
[2]Hypocalcemia (serum calcium <7 mg/dl)
[3]Hyperglycemia (serum glucose >150 mg/dl)
[4](pH <7.25 and base deficit >12 mmol/L)

Table IV. Clinical Outcomes

	LDPN group (n=45)	HDPN group (n=51)	p
RDS, n (%)	30 (66.7%)	38 (74.5%)	0.501
Sepsis (culture positive), n (%)	31 (68.9%)	23 (45.1%)	0.024
NEC (stage ≥2), n (%)	20 (44.4%)	9 (17.6%)	0.007
PDA, n (%)	20 (44.4%)	18 (35.3%)	0.407
IVH (grade ≥3), n (%)	7 (15.6%)	3 (5.9%)	0.182
PVL n (%)	2 (4.4%)	9 (17.6%)	0.056
ROP (stage >2), n (%)	4 (8.9%)	11 (21.6%)	0.100
BPD, n (%)	18 (40.0%)	21 (41.2%)	1.000
Cholestasis, n (%)	3 (5.9%)	6 (13.3%)	0.297
Length of stay (days) mean ± SD	48.24 ± 20.93	52.82 ± 28.62	0.846
Mortality, n (%)	6 (13.3%)	3 (5.9%)	0.297

RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, IVH: intraventricular hemorrhage, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia.

the improvement in growth found in our study. In addition, the mean duration of parenteral nutrition, mean number of days to reach full enteral feeding and incidences of sepsis and necrotizing enterocolitis were significantly lower in the HDPN group. In the meta-analysis by Moyses et al.[7], the duration of parenteral nutrition was not different between groups, and the estimated risk of sepsis, although nonsignificant, was lower in the early parenteral nutrition group. In the studies by Can et al.[9], Valentine et al.[16] and Donovan et al.[21], infants in the early and aggressive parenteral nutrition groups had shorter durations of parenteral nutrition and reached full enteral feedings sooner than infants in the conservatively managed groups. Also, Kotsopoulos et al.[20] documented reduction in the incidence of sepsis with early amino acid administration, and Drenckpohl et al.[17] documented reduction in the incidence of necrotizing enterocolitis with higher rates of lipid infusion. Based on this data, we can suggest that improved nutritional intake resulting in better host defenses reduces the risk of sepsis and necrotizing enterocolitis. As the incidence of sepsis and necrotizing

enterocolitis decreases, the time to achieve full enteral nutrition decreases. Reduction in the requirement for venous access further reduces the risk of sepsis. Likewise, early full enteral feeding and decreased incidence of sepsis and necrotizing enterocolitis in the HDPN group may also have contributed to the better growth outcomes at discharge in our study.

Several studies have demonstrated that earlier and higher intakes of amino acids and energy were unassociated with metabolic disturbances[6, 9-11, 15-18, 20, 23-25, 27-29]. Similar to what was found in previous studies, we noted higher serum BUN levels on the second day of life in the HDPN group[15, 18, 20, 23, 29]. This may be related to higher protein turnover and increased oxidation of amino acids. In addition, we noted lower rates of hypoglycemia and hypocalcemia in the HDPN group.

As in most other reports, there was in our study no difference in mortality or morbidity, or in incidence of patent ductus arteriosus, intracranial hemorrhage grade 3-4, periventricular leukomalacia, retinopathy of prematurity, bronchopulmonary dysplasia or cholestasis[7]. These findings indicate that an improved parenteral nutrition regimen is not associated with a higher incidence of adverse clinical outcomes.

Our study has some limitations. First, patients could not be randomly assigned; however, it is not ethical to limit parenteral nutrition in a selected group of preterm infants. Another limitation of our study was that long-term growth and clinical outcomes were not assessed after discharge.

In conclusion, in this study, patients who received higher-dose parenteral nutrition showed reduced postnatal weight loss and time to regain birth weight, improved subsequent postnatal growth, decreased duration of parenteral nutrition, enhanced achievement of full enteral feeding and decreased incidence of sepsis and necrotizing enterocolitis. However, long-term growth and neurodevelopmental outcomes need to be investigated in further studies.

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