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Effect of Different Approaches to Intravenous Nutrition on the Pattern of Weight Gain in Very Low Birth Weight Preterm Neonates: A Randomized Clinical Trial

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ABSTRACT

Background: Low birth weight neonates have low energy reserves; thus, postpartum feeding is required to meet their ongoing nutritional requirements. Total parenteral nutrition (TPN) provides critical nutrients for the metabolism and development of neonates; however, few studies have investigated the effect of TPN on the early growth patterns of neonates. The present study examined the effects of TPN on preterm neonate anthropometric characteristics using two commonly used TPN calorie introduction techniques.
Methods: This randomized clinical trial studied preterm neonates with birth weights of less than 1500 g. Calories were initiated at a rate of 3 g/kg for lipids and 3.5 g/kg for amino acids in the intervention group. In the control group, the amino acid solution was begun at 1 g/kg/day and the lipid solution at 0.5 g/kg/day, and both were increased daily by 1 g/kg to a maximum of 3.5 and 3 g/kg/day for amino acids and lipids, respectively. In this group, all neonates reached full calorie intake at 3 to 5 days of age. The trend of change in the anthropometric parameters was evaluated and compared.
Results: Although both groups showed an increase in neonatal weight, length and head circumference, no statistically significant difference was observed between them. Both groups had similar lengths of hospital stay.
Conclusion: Based on the findings of the present study, TPN feeding done using two approaches to amino acid and lipid administration had no significant influence on hospital stay, TPN duration, or growth indices in preterm neonates weighing less than 1500 g.

Keywords: ---------------

Introduction

Nutritional care for hospitalized neonates has long been a key difficulty in neonatal medicine, particularly when the neonates are unable to receive their nutritional needs orally due to prematurity or illness. As premature neonates born before 34 weeks of gestation lack development of the swallowing, breathing, and sucking processes, they are unable to be fed orally or enterally (1). Except for forceful sucking, oral feeding requires coordination between swallowing, epiglottal constriction of the larynx and nasal passageways, and normal esophageal movement. This coordinated process is not visible before 34 weeks of pregnancy (2).

When the neonatal gastrointestinal tract is unable to supply the required nutrients, they must be administered intravenously. Many such neonates have already experienced irreversible

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physical, neurological, and developmental damage as a result of insufficient dietary intake. The administration of fluids containing the nutrients, electrolytes, minerals, and vitamins necessary for neonate metabolism and development is known as total parenteral nutrition (TPN). The TPN can be used as the sole source of nutrition or as a supplement to breastfeeding (3). The goal of TPN is to reduce the loss of energy reserves in the body while providing the nutrients required for growth and development.

As long as they tolerate oral feeding, intravenous nutrition can play a significant role in the treatment of unwell neonates, as it can reduce metabolic problems and limit the disruption of normal neonatal growth. Intravenous or intestinal feeding should be started within 24 h of birth. Any neonate who is unable to tolerate intestinal feeding for longer than 2-3 days should be fed intravenously. This feeding method has saved the lives of neonates with extremely low birth weights (ELBW) as well as those with refractory diarrhea syndrome or extensive intestinal resection. The infusion can be given percutaneously or, in rare cases, through a central or peripheral venous catheter (4, 5).

The maximal intrauterine growth of the body and brain occurs at 34-40 weeks of gestation, which is the time that most very low birth weight (VLBW) and premature babies are born. Because these neonates have very low internal reserves, rapid administration of TPN is required to reach a growth rate that is comparable to intrauterine growth. The TPN should begin as soon as possible to prevent postnatal growth retardation and improve nerve development (6). The American Academy of Pediatrics states that an energy equivalent to 120 kcal/kg/day is required for neonates receiving oral nutrition and an energy equivalent to 80-100 kcal/kg/day and protein equivalent to 3-4.5 g/kg/day is required for neonates receiving TPN support (7-9).

Most preterm neonates gain less weight compared to fetuses of similar gestational age. As a result of this growth retardation, the weight of many such neonates will remain below the 10th percentile of gestational age into childhood, which will have negative consequences for subsequent neurodevelopment. A rapid weight increase before 40 weeks of pregnancy, on the other hand, is linked to better neonate outcomes (10). Several strategies have been proposed for the onset of TPN feeding according to scientific sources. Some sources recommend a gradual increase in calories (11), and others recommend a rapid increase in calories (12). However, few studies have looked at the effects of TPN, particularly caloric intake, on the early growth patterns of these neonates. The current study examined the effect of TPN on the anthropometric measures of preterm neonates using these two approaches to the introduction of a sudden and gradual increase in calories.

Methods

This randomized clinical trial was conducted on preterm neonates with birth weights of less than 1500 g who were admitted to Hajar Hospital in Shahrekord, Iran, in 2020. Neonates weighing less than 1500 g who received TPN and survived for at least seven days were included in the study. Those who were referred after the third day of birth as well as those with major congenital anomalies, syndromic features, severe illness, TPN complications (triglyceride above 200 mg/dL or Blood Urea Nitrogen above 50), inability to be detached from mechanical ventilation for interventions, such as weight gain, or death before TPN completion were excluded from the study. The sample size was calculated at 30 neonates for each group based on the sample size calculation formula with 95% confidence and 90% test power. For randomization, each neonate was assigned a number, after which a random list of numbers was generated using random number generator software as:

$$n = \frac{2(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 SD^2}{d^2} = 30$$

Where = 0.05, β = 0.2, D = 0.5, and SD = 0.7.

The neonates were separated into control (n=30) and intervention (n=30) groups. According to the TPN nutrition guidelines, 70 to 80 ml/kg of fluid per day was administered on the first day. This was raised daily by 20 ml/kg/day until a volume of 150 ml/kg/day was reached. Dextrose was given for the first two days of life, followed by electrolytes on the third day. On the first day of life, dextrose was infused at a rate of 6 mg/kg/min and was adjusted to randomly adjust blood sugar levels at 60 to 120 mg/dL. Sodium was prescribed at 3-5 meq/kg/day and potassium at 2 meq/kg/day based on the serum electrolyte levels, which were measured twice a week.

Calories were initiated at a rate of 3 g/kg for lipids (20% intralipids) and 3.5 g/kg for amino acids (10% amino acids) in the intervention group. The amino acid solution (10% amino acids) was begun at 1 g/kg/day, and the lipid solution (20% intralipids) at 0.5 g/kg/day in the control group and the values were increased daily by 1 g/kg to a maximum of 3.5 and 3 g/kg/day for amino acids and lipids, respectively. All the neonates in this group were able to consume all of their calories in 3 to 5 days.

The amino acids and lipids were given separately, and a PICC line was used for lipid infusion. If a neonate was receiving phototherapy, the lipids were kept away from light. The bottles and tubes were replaced every 24 h. During treatment, biochemical and hematological markers were examined. Every two weeks, serum electrolytes and kidney function tests were performed. On day four, a blood gas analysis was performed. Once a week, liver function, total cholesterol, and triglyceride tests, as well as a complete blood count, were conducted. In this study, the following procedures were considered:

- With an increase in the triglyceride level to 170 to 200 mg/dL, the lipid solution was reduced by 0.5 g/kg per day.
- Lipid administration was discontinued if the liver enzymes increased to more than triple the normal value or the triglyceride level surpassed 200 mg/dL.
- If the creatinine level increased abnormally, the amino acid administration was discontinued.

If not contraindicated, breast milk was given to the neonate from the third day of life. Enteral feeding was delayed if breast milk was not available. Enteral feeding began at 10 to 20 ml/kg/day, as tolerated by the neonate. When enteral feeding reached 100 ml/kg/day, TPN feeding was discontinued. Nutritional data such as infusion solution type and volume, parenteral nutrition composition, enteral nutrition type and volume, and other additives were recorded. The weight, length and head circumference of the neonates were measured at birth, weekly, at discharge, and at 40 weeks after birth.

The duration of hospitalization and onset of enteral feeding were recorded for each neonate. The data were summarized for each group using frequency and percentage for qualitative variables and using the mean ± standard deviation for quantitative variables. The normality distribution was assessed using the Kolmogorov-Smirnov test. Differences between variables in the intervention and control groups were analyzed using the independent t-test and Chi-square test. The differences between variables between groups at different times were analyzed using the multivariate test. As the variables were measured more than twice in each group, both intragroup and intergroup comparisons were made. Statistical significance has been defined as $P < 0.05$ in all tests, and analysis was performed by SPSS (version 21). The Ethics Committee of Shahrekord University of Medical Sciences provided the study with a Code of Ethics (IR.SKUMS.REC.1399.097).

Results

The current study comprised 78 neonates weighing less than 1,500 g who were admitted to the NICU of Hajar Hospital in Shahrekord, Iran and who were TPN candidates. Due to serious illness, eighteen neonates were removed from the study (1 case of Down syndrome, 12 cases of sepsis, 1 case of heart failure, 3 cases of meningitis, and 1 case of necrotizing enterocolitis). The remaining 60 neonates were randomly and evenly assigned to the control and intervention groups (Figure 1). No increase in the triglycerides, liver enzymes or creatinine levels were observed in any of the neonates.

No statistically significant difference was observed in the frequency distribution for gender, mode of delivery, underlying maternal disease, or gravida in the study groups. In addition, no statistically significant differences were found between groups for mean gestational age, mean anthropometric parameters, length of hospital stay, and length of TPN administration (Table 1). While there was an increasing trend in neonatal weight in both groups, this trend was not significantly different (P=0.172). Although the intervention and control groups had similar increases in length, the neonatal length increase trend was insignificant between groups (P=0.136). Both groups experienced increases in head circumference during the study period; however, the difference was not significant between groups [P=0.073; Table 2].

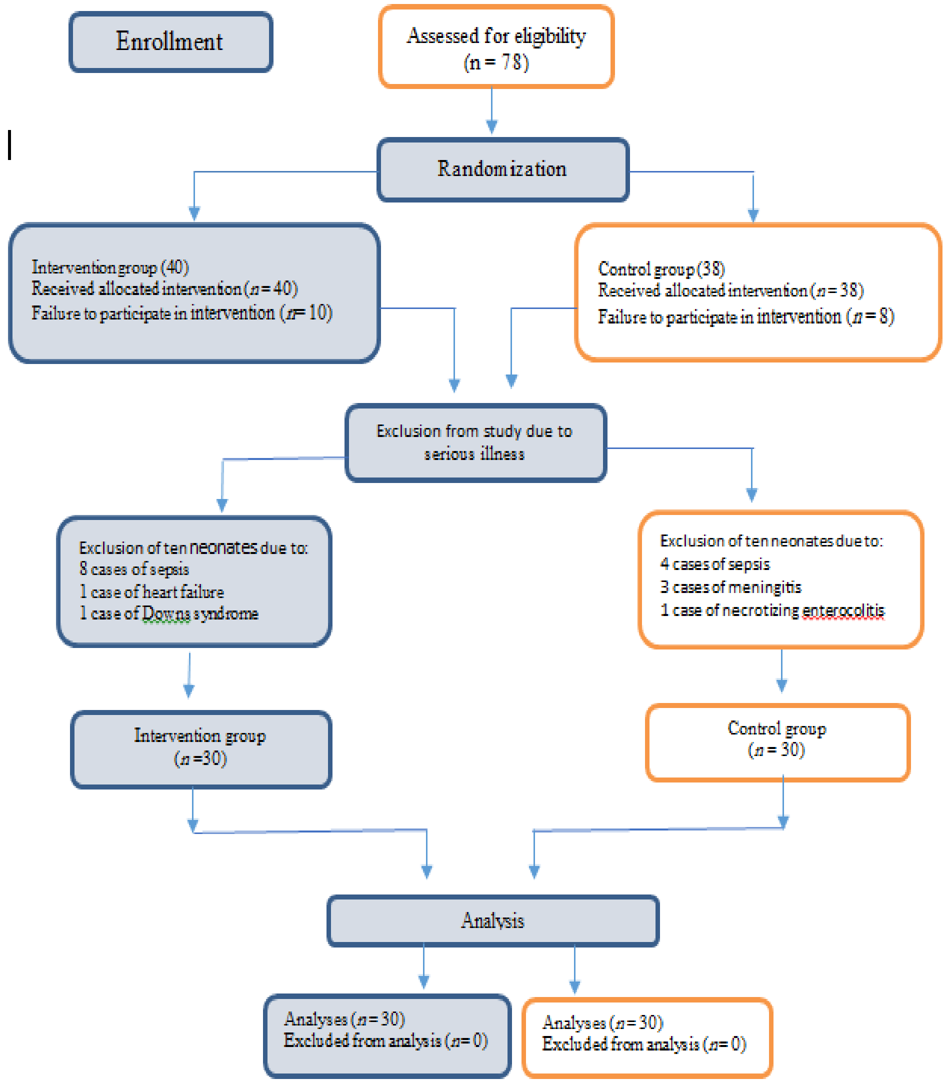

Figure 1. Consort diagram of the number of neonates and reasons for their exclusion from the intervention phase in the intervention and control groups

Table 1. Baseline Characteristics in the intervention and control groups

Characteristics	Intervention group	Control group	*P*-value
Male gender (%)	17 (56.7)	12 (40.0)	0.301
Mode of delivery (%)			0.612
Normal delivery	1 (3.4)	3 (10.0)	
Cesarean section	28 (96.6)	27 (90.0)	
Underlying disease of the mother (%)	21 (70.0)	15 (50.0)	0.187
Gravid			0.143
1	6 (20.0)	10 (33.3)	
2	19 (65.5)	11 (33.3)	
3	5 (17.2)	6 (20.0)	
6	0 (0.0)	1 (3.3)	
7	0 (0.0)	2 (6.7)	
Mean gestational age (week)	30.76±3.00	30.50±1.28	0.189
Mean birth weight (g)	1315.16±155.68	1278.33±180.00	0.567
Mean length (cm)	39.20±2.56	37.73±3.90	0.156
Mean head circumference (cm)	28.10±1.71	29.20±4.73	0.901
Mean length of hospital stay (d)	19.50±5.23	19.20±5.77	0.976
Mean time for TPN (d)	12.80±5.19	11.62±4.25	0.410

Table 2. Anthropometric parameters in low birth weight preterm neonates in intervention and control groups

Characteristics	Control group	Intervention group	P-value(independent sample t test)
Weight			
Day 1	1315.16±155.68 g	1278.33±180.00 g	<0.001
Day 7	1299.16±229.01 g	1109.00±157.72 g	<0.001
Day 14	1455.42±242.91 g	1281.00±180.45 g	<0.001
Day 21	1623.25±244.34 g	1465.00±183.74 g	<0.001
At discharge	1835.00±160.82 g	1691.00±159.33 g	<0.001
Week 40	3275.00±192.47 g	3210.00±237.81 g	<0.001
P-value	<0.001	<0.001	<0.001
Length			
Day 1	39.20±2.56 cm	37.73±3.90 cm	<0.001
Day 7	39.22±3.48 cm	38.75±3.10 cm	<0.001
Day 14	40.59±2.21 cm	39.71±3.19 cm	<0.001
Day 21	41.41±2.23 cm	40.12±3.16 cm	<0.001
At discharge	42.29±1.41 cm	41.42±3.24 cm	<0.001
Week 40	50.31±2.25 cm	47.57±3.63 cm	<0.001
P-value	0.024	<0.035	
Head circumference			
Day 1	28.10±1.71 cm	28.10±1.69 cm	0.12
Day 7	28.59±1.98 cm	28.78±1.78 cm	0.85
Day 14	29.12±1.94 cm	29.50±1.48 cm	0.66
Day 21	29.79±1.66 cm	29.98±1.44 cm	0.11
At discharge	30.11±1.78 cm	30.60±1.54 cm	0.36
Week 40	34.18±1.50 cm	34.16±1.16 cm	0.54
P-value	<0.09	<0.11	

P-value is associated with repeated measure

Discussion

The goal of TPN is to achieve complete intestinal nutrition in the shortest amount of time while maintaining optimal growth and nutrition and avoiding the negative consequences of the rapid onset of oral feeding. Although some evidence suggests that enteral administration of amino acids and lipid solutions is well tolerated by VLBW neonates in the first days of life (9, 12), their nutritional needs at this time remain unknown. In the current trial, the timing of the TPN protocol was similar in both the intervention and control groups, and there were no differences in the trend of change in the anthropometric indices, such as body weight, length and head circumference between groups. This indicates that both feeding approaches provided comparable growth rates for neonates, and the duration of TPN was comparable in both methods.

Sivamurthy et al. (13) studied neonates with gestational ages of 23 to 33 weeks with birth weights of 501 to 1500 g. Their goal was to determine how VLBW neonates responded to a more rapid increase in amino acid dosage during their first few days of life. Their results revealed that the increased amino acid regimen had no negative consequences. In the first month after birth, VLBW neonates may be able to tolerate even higher dosages.

Clark et al. (14) randomly allocated preterm neonates (23-29 weeks) into two groups in a multicenter study. In one group, amino acid supplementation began at 1 g/kg/day and was gradually increased to a maximum of 2.5 g/kg/day. In the other group, amino acids began at 1.5 g/kg/day and were gradually increased to a maximum of 3.5 g/kg/day. The findings revealed that growth up to 28 days after birth and the incidence of secondary diseases were similar in both groups. Although one group received more amino acids during TPN, the growth rates of the two groups were not significantly different.

A systematic meta-analysis of 14 studies found that high amino acid dosages (>3 g/kg/day) or early onset of amino acid administration (within 24 hours) were safe and feasible in preterm LBW neonates. However, although it was acceptable, it provided no significant growth benefits (15), which is in line with the findings of the current study. The hospitalization duration, TPN duration, and neonatal growth indices were not significantly different between groups in the present study.

Blanco et al. (16) examined 61 neonates, 31 in the standard amino acid (AA) group and a total of 30 in the early and high AA groups. The results showed that the mental developmental index (MDI) and psychomotor developmental index values were similar between groups; however, the early and high AA groups scored lower MDI values at 18 months. At two years of age, this difference had vanished. In most follow-up visits, the early and high AA group means for weight, length and head circumferences were significantly lower than for the standard AA group. The MDI and postnatal growth values were negatively linked with cumulative and single plasma AA concentrations. According to the data, extremely LBW neonates who received early and high intravenous AA during the first week of life recorded low overall growth at two years of age.

The results of Bulbul et al. (17) revealed that, while earlier, more aggressive administration of amino acid (AA) and lipids were not associated with significant metabolic abnormalities, and the growth rates and plasma AA concentrations were similar to those of neonates whose were given AA and lipids on the first day of life. To reduce malnutrition and improve neonatal outcomes, the current guidelines for preterm neonates recommend increased parenteral nutrition. However, there is a paucity of evidence addressing the long-term efficacy of this method. In the first week of life, high-energy intake by parenteral feeding has little influence on neonatal outcomes, such as morbidity or length of hospital stay.

Energy-enhanced parenteral feeding may have an effect on long-term neurodevelopment in premature neonates (18). In the present study, the results of the different approaches to the administration of amino acids and lipids in TPN neonates were not significantly different for the hospital stay, TPN duration, or neonatal growth indices. However, because discrepancies exist in some studies regarding the efficacy and side effects of various nutritional approaches, more studies and longer follow-up periods should be done to verify the efficacy of these administration methods.

Conclusion

The current study found that the results of TPN feeding using two approaches of amino acid and lipid administration had no significant effect on hospital stay, TPN duration, or growth indices in preterm neonates weighing less than 1500 g. This indicates similar levels of efficacy for the two approaches for preterm neonates.

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Conflicts of interest

The authors do not have any conflict of interest.

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