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The Impacts of Varying Protein and Energy Intakes on the Growth of Neonates with Very Low Birth Weight : An Experimental Study

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ABSTRACT

Background: Studies have indicated contradictory results concerning the impact of protein-based diets on very low birth weight neonates. Hence, this study explored the impacts of various calorie and protein diets on the growth of very low birth weight neonate during 15 days.

Methods: This study was carried out on 44 neonates with very low birth weight, selected regarding the inclusion criteria. They were assigned into two clusters based on their birth weight. Each cluster included a control group receiving the standard diet formula, and an experimental group with neonates weighing 1000-1500gr who followed a high-energy diet with 4gr protein and those weighing less than 1000gr who received a high-energy diet with 4.2gr protein. Finally, the neonates' weight, height, and head circumference were measured every 3 days for 15 days.

Results: According to the findings, the mean weight of the neonates who weighed between 1000 and 1500gr was higher in the intervention group from the third day after initiating the diet, though no significant difference was observed. Similarly, the mean weight of intervention group in the second cluster was higher than the neonates in the control group from the third day with a statistically significant difference on the 15th day. Moreover, no significant difference was found in other measurements between groups.

Conclusion: The results demonstrated the effect of a higher weight of protein intake group on the 15th day. Hence, it recommends providing higher protein intake formula to lower infant birth weight for better growth.

Keywords: High calories, High protein, Neonate, Very low birth weight

Introduction

Adequate nutrition to meet the nutritional needs of preterm neonates, particularly the very low birth weight (VLBW) ones, is apparently important (1). These neonates are nutritionally high risk because the fetus needs more nutrients in the last three months of pregnancy. VLBW neonates are born with minimum fat and body mass, so they are prone to deficiency of energy and protein (2,3). The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published the Enteric Nutrition (EN) Recommendations for premature neonates in 2010. These consist of daily provision of 110-135 calories and 4.4 to 4.5 grams of protein per kilogram. Neonates weighing <1 kg need more calories and protein (4).

The American Academy of Pediatrics recommends breastfeeding for every neonate

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irrespective of their birth weight and asserts that premature neonates should receive breast milk (MOM) or donor's breast milk (DBM) (5). Human milk (HM) boosts the function of immune system, increases gastrointestinal maturity, and reduces the risk of early complications, including necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and early retinopathy. In addition, using HM improves physical and mental development and reduces the metabolic syndrome risk (6, 7). Although it is the most required nutrition for VLBW neonates, it does not provide sufficient calories and protein for premature neonate growth (8). Finally, HM's amount of calories and protein is not established well (9).

On the other hand, because of the time of donor milking and pasteurization, milk reduces the number of microbes before consumption in DBM, reducing the nutrients. Furthermore, it reduces important immune and growth factors, including immunoglobulins, cytokines, lactoferrin, and insulin (10, 11).

Proper nutrition is necessary for the premature baby's optimum growth and development. Protein is one of the most important components of acceptable nutrition, providing the necessary amino acids for the synthesis of protein, which is essential for growth (12). VLBW neonatal nutritional management has received considerable attention in the United States and Europe since 2000. There are two ways to estimate the amount of protein needed by premature neonates: estimation considering the amount of protein intake of neonates and estimation regarding the theoretical calculations (factorial approach). Premature neonates have a speedy growth rate and protein accumulation (13), so it is important to control the amount of protein intake in neonates with less than 2.5 kg birth weight and have formula fed. Consuming excess protein raises the level of blood urea and amino acid (phenylalanine), damaging nerve development. Excessive protein intake may restrict the neonates' growth (13). There are three stages of nutritional support in premature neonates: (1) early invasive feeding during the first few weeks after birth, when they are at the most fragile stage (acute stage), (2) human fortified milk (HMF) or early formula for the middle period when neonates usually progress slowly to full intestinal feeding but potentially can be an opportunity for significant growth (growing care stage), and (3) the post-discharge phase (14-18).

Higher protein intake has some potential risks, including elevated amino acids concentrations, hydrogen ions, and urea due to the preterm neonates' immature amino acid metabolic pathways. They may not be capable of handling the increased protein level effectively. Therefore, metabolic acidosis and higher levels of amino acids such as tyrosine and phenylalanine may be observed in plasma (13). Such metabolic changes could theoretically result in mental retardation. In addition, early feeding induces adaptive responses to endocrine and metabolic homeostasis, leading to "metabolic planning," which changes the long-term consequences of chronic disease. Renal hypertrophy has been reported with increased growth hormone such as insulin-growth factor 1 in response to high protein intake (13). Excessive protein consumption early in life may rise the risks of obesity and adverse increase in fat mass (19) and other pathologies such as diabetes. Therefore, the long-term consequences of primary nutrition should be considered (13).

High protein intake has some advantages, including the adequate amount of protein for the lean tissue growth, bone and blood cells growth, hormones and enzymes synthesis, and the inflammatory pressure maintenance. Protein deficiency leads to stunted growth in neonates and, if severe, it can result in edema and lower infection resistance (13).

To achieve evidence-based nutritional protocols, oral nutrition is preferable to complete intravenous feeding (TPN) because it leads to faster withdrawal of vascular catheters, followed by reduced sepsis and other catheter-related complications, as well as adverse effects of TPN and starvation (20-23). Energy stored as carbohydrates is more effective than the energy which is supplied as fats oxidizing crude protein in low-birth-weight neonates (24). In food intake, carbohydrates are higher in fat growth and protein in LBW breastfeeding, which is eaten orally more than fats. The main goal of VLBW neonates during feeding is to achieve complete nutrition as soon as possible to maintain optimal growth and nutrition and prevent the adverse consequences of nutritional progression. A multidisciplinary working group at McMaster University (consisting of clinicians, nutritionists, nurses, breastfeeding counselors, and occupational therapists) performed a structured search and provided practical suggestions for VLBW nutrition (25). Due to the mentioned cases and the contradictory results of various studies working on the impact of a protein-based diet on neonates with VLBW, this study aimed to investigate the impact of different calorie and protein diets on the growth of VLBW neonates in Imam Ali and Kamali Hospitals in Alborz.

Methods

The present study was an experimental study conducted in 2022 in Kamali and Imam Ali Hospitals in Alborz Province, which are among the most well-equipped neonatal intensive care units in the country. Study cases were neonates with very low birth weight and no complications (fever, sepsis, etc.). Exclusion criteria included neonates with IUGR, in need of oxygen, with chronic disease, with any chromosomal abnormalities or defects, and the reluctance of parents of research units to participate in research at any time during the study. The sample size was calculated 44 neonates based on similar studies with 95% confidence interval, error coefficient of 0.05, and effect size of 0.5, using the sample size determination formula (26).

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2}$$

Initially, neonates' baseline data, including birth age, birth weight, birth head circumference, birth height, type of delivery, sex of the baby, whether or not corticosteroids were taken during pregnancy, and first and fifth-minute Apgar scores, were collected through a demographic questionnaire. Samples were selected by availability from two hospitals in Karaj and were assigned into two groups according to their weight (neonates with 1000 to 1500(group1) and neonates with less than 1000 gr weight (group2)). Then, using random blocks of six, they assigned the participants into two intervention and control groups.

This study was a one-sided blind study. That is, the parents of the neonates were informed about the purpose of the study but they were not aware in which group their neonate was placed. Also, the person who measured the neonates' weight, height, and head circumference did not know the type of neonate nutrition. The standard formula diet for preterm neonates was given to two control groups (a and b). For the experimental group (c) received the formula with calories up to 130 kcal / kg per day with protein 4 gr / kg per day, and the experimental group (d) had the formula with calories up to 135 kcal / kg/day with protein 4.2 gr / kg/day.

Before starting oral feeding, all groups received intravenous feeding with a mixture of 3 gr / kg amino acid, 1 gr / kg interralipid, and 80 cc / kg 10% glucose serum. Oral feeding started from the second day as MEF, and after feeding tolerance oral 50 cc / kg intravenous feeding was completed. Oral breastfeeding was continued with the formula for each group.

Then, each neonate's weight, height, and head circumference were measured every 3 days for 15 days by a researcher who used an electronic weight scale with an accuracy of 10 grams and a non-stretching tape.

SPSS software version 22 was employed to analyze the data. First, the Kolmogorov–Smirnov test was run to determine the data normality, and T-test was used to compare quantitative data. Data were reported as standard with 95% confidence interval and a $P<0.05$.

The most crucial limitation of the present study was the reluctance of patients' parents to participate in the study; however, the researcher could overcome this issue to a large extent while explaining the plan to them and gaining their satisfaction and trust.

Ethical approval

Research started after receiving the Ethics Committee approval in Medical Research with code (IR.ABZUMS.REC.1398.195) and a written letter of introduction from Alborz University of Medical Sciences.

Results

Regarding gender, 25 neonates (56.8%) were boys, and 19 neonates (43.2%) were girls. In terms of the type of delivery, 14 neonates (31.8%) were born through normal delivery, and 30 (68.2%) through cesarean section. Regarding prenatal corticosteroid use, 31 neonates (70.5%) received corticosteroids, and 13 (29.5%) did not. Table 1 lists the neonates' demographic characteristics by clusters.

To evaluate the impact of a high-calorie and protein-rich diet on neonates' weight gain, height, and head circumference, an independent t-test was used after examining the data normality. Despite the changes in the mean height and head circumference of neonates after 15 days of being fed with the study diet in the experimental group, no significant difference was observed ($p> 0.05$).

By examining the effect of diet on neonatal weight, it was found that the average neonatal weight had an upward trend from the start day onwards; however, this difference is significant in neonates who weigh less than 1000 grams at

Table1. Demographic characteristic of participants

Cluster (By Weight)	Group		N	Mean	Std. Deviation	p-value
Neonates with 1000 to 1500 gr weight	First minute Apgar	Intervention	11	4.63	2.94	0.5
		Control	11	4.00	2.40	
	Gestational age	Intervention	11	30.45	2.62	0.5
		Control	11	29.90	1.75	
	Five minute Apgar	Intervention	11	7.09	2.3	0.2
		Control	11	5.9	2.3	
Neonates with less than 1000 gr weight	First minute Apgar	Intervention	11	6.18	2.48	0.1
		Control	11	4.36	3.07	
	Gestational age	Intervention	11	29.72	1.42	0.4
		Control	11	30.27	1.42	
	Five minute Apgar	Intervention	11	7.5	2.5	0.7
		Control	11	7.1	2.6	

birth, showing its positive effect (Table 2).

Finally, it should be noted that during the study, the patients' BUN levels were checked in three stages (once every 5 days) from the beginning of the study, and there was no evidence of azotemia in the patient.

Table 2. Result of Height, Weight and head circumstance since start of study until 15 days after in two group of study

			Group Mean±SD		
			Control	intervention	P-value*
Neonates with 1000 to 1500	Weight	Birth weight	1236.7±139.32	1224.7±164.20	0.85
		Start of study	1377.2±133.09	1361.9 ± 159.3	0.81
		15 days after	1622.2±136.8	156.5±1717.6	0.14
	Height	Birth Height	38.5±1.52	38.3±1.18	0.74
		Start of study	41.3±1.7	41.2±1.5	0.84
		15 days after	42.9±1.7	42.8±1.5	0.88
	Head circumstance	Birth	27.3±0.74	27.1±0.77	0.45
		Start of study	28.8±0.0.85	28.7±1.04	0.87
		15 days after	30.05±0.86	30.61±1.08	0.19

			Control Mean± SD	Intervention Mean± SD	P-value
Neonates lower 1000gr	Weigh	Birth weight	886.1±68.6	848.2±103.7	0.32
		Start of study	1016.5±67.9	989.5±105.2	0.48
		15 days after	1271±65.5	1365.9±98.7	0.01
	Height	Birth Height	36.6±1.04	37.1±1.15	0.6
		Start of study	39.1±1.13	40±1.3	0.13
		15 days after	41.1±1.1	42.03±1.3	0.8
	Head circumstance	Birth	27.1±0.7	27.1±0.7	0.8
		Start of study	28.4±0.9	28.5±1.2	0.8
		15 days after Birth	29.8±0.9	30.3±1.3	0.2

Discussion

This study aimed to explore the impact of diets with various calories and protein on the neonatal growth in 44 neonates with birth weights of 1000-1500 gr. According to the results, the average neonatal weight in the intervention group was greater than that of the control group from the third day after treatment (1), though no statistically significant difference was observed. However, a significant difference would be obtained if the study was continued. In contrast, the mean weight of neonates in the intervention group was greater than the control group from the third day (2), and there was a statistically significant difference on the 15th day. Conversely, no statistically significant differences were found between the groups regarding height and head circumference.

Nicholas et al. conducted a study in 2005, demonstrating VLBW neonates with high protein intake (3.3 gr / 100 kcal) had a significantly higher mean neonatal weight at 12 weeks in this group than the controls (27). The results of our study showed the same effect because the average weight of neonates in the intervention group was significantly higher than the control group on the 15th day in those with a birth weight below 1000 gr.

Unlike the present study, Cooke et al., in a 2006 study, revealed that the average weight of high-protein VLBW neonates (3.6 gr / 100 kcal) was significantly higher than the control group without any metabolic complications in these neonates (28). Similar to the present study, Costa et al.'s study for 28 days demonstrated that the average weight of VLBW neonates receiving protein 4.7 gr / kg/day and 4.2 gr / kg/day was significantly greater than those receiving standard formula (29). Moreover, Costa et al., found no significant difference in terms of neonatal height, which agrees with the results of the present study. Yet, regarding the head size in their study, it was more significant than the control group (29). Another study by Ditzen et al. (2013) showed that the weight, height, and head circumference of high-protein, high-calorie VLBW neonates did not differ significantly from neonates receiving the standard formula but weight gain in ELBW neonates was significantly more than the control group, which indicates the importance of nutrition in these neonates to help with nutritional failure (30), confirming the findings of the present study. The study results revealed that the average weight of neonates with birth weight less than 1000 grams receiving high-protein and -calories formula was significantly higher than the control group. Still, no significant difference was observed in height and head circumference. In this regard, further studies are required in this field to improve the nutritional status and growth of VLBW neonates, especially those with a birth weight of less than 1000 grams. Neonates should be examined for weight, height, head circumference, body fat mass, and metabolic criteria in a multicenter clinical trial to examine the effect of diets with different proteins and calories over 6 months.

Conclusion

This study showed the effect of a higher weight of protein intake group on the 15th day. So, it is better to introduce higher protein intake formula to lower infant birth weight for better growth.

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Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical consideration

Research started after receiving the Ethics Committee approval in Medical Research with code (IR.ABZUMS.REC.1398.195) and a written letter of introduction from Alborz University of Medical Sciences. Then, the objectives of the project and confidentiality of the research information was explained to the patients' parents to attract their cooperation. Finally, they were asked to complete the informed consent form in case they agreed to take part in the study.

To prevent kidney complications in neonates, BUN was checked 3 times (every 5 days) during the study with other blood samples if possible; otherwise, it was performed separately. About 2 cc of blood was taken at each stage, and if an increase in BUN was observed more than normal, serum therapy and prerenal azotemia treatment were performed. If this process continued, the neonate was excluded from the study, and his diet was changed to standard. Peritoneal dialysis was performed at the discretion of the pediatric nephrologist. If all these measures were needed, the researcher would bear the cost.

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