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IMPACT OF PROTEIN AND CARNITINE CONSUPTION ON OUTCOMES OF CARE DEVELOPMENT OF FULL-TERM NEWBORNS WITH CRITICAL PERINATAL DISEASES

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Abstract. Impact of protein and carnitine consuption on outcomes of care development of full-term newborns with critical perinatal diseases. Anikin I.O., Varynskyi B.O., Stryzhak L.S., Serhieieva L.N., Snisar V.I. *There were studied results of the impact of increased consumption of proteins and L-carnitine in the nutrition program of full-term newborns with perinatal diseases on the results of physical development and inpatient treatment features. The purpose of the work was to study the correlations between short-term higher consumption of protein and carnitine by full-term newborns and the results of their physical development, the duration of hospital care development. The vital signs of 59 full-term newborns were studied in a randomized controlled trial in the period 2017-2020. The main critical disease of the perinatal period in newborns of both groups was found to be hypoxic-ischemic encephalopathy of a moderate degree in 86.7% and 86.2%, without a statistically significant difference. One group (n=30) received nutrition with mother's milk or formula, the second group (n=29) received similar nutrition with fortification with a protein and L-carnitine supplement during the hospital stay. At the beginning and at the end of the treatment, physical development of the newborns was studied and correlations between the obtained data were investigated. Newborns of both groups did not differ in characteristics at the beginning of the study. The proportions of the newborns' weight corresponded to the limits of the 50% percentile. The group with increased consumption of protein and carnitine, fortification group (FG) demonstrated better indicators of physical development, they regained body mass faster. Body mass of the newborns of the fortification group goup was 3966.9±439.1 g, compared to the standard nutrition (SN) group, with indicators being 3554.6±452.3 g, at p=0.003. The rate of increase in body length in FG was twice that of the SN group. Consumption of a larger dose of protein was accompanied by a shorter stay in the intensive care unit – 10.0 (8.0; 12.0) days versus 12.0 (11.0; 16.0) days, with U=235.0; p=0.002; earlier discharge from the hospital – 21.0 (19.0; 27.0) days versus 26.5 (22.0; 31.0) days, with U=267.0, p=0.01. Carnitine supplementation in the FG group led to an increase in the level of free carnitine in the blood plasma samples taken before the discharge from the hospital. The study of correlations revealed a positive correlation between the consumption of a full dose of proteins and the total increase in height (R=0.3, p<0.05), the increase in body weight (R=0.3, p<0.05). A negative correlation was found between the protein level and the duration of treatment in the hospital (R= -0.3, p<0.05). The level of free carnitine had a positive effect on the increase in body length (R=0.51, p<0.05), daily weight gain (R=0.3, p<0.05). A poor increase in body length was associated with a longer duration of respiratory support: the correlation had an inverse direction R= -0.4, p<0.05. Improving nutritional strategies has significant prospects for improving care development of full-term babies with critical perinatal states.*

Реферат. Вплив споживання протеїну та карнітину на результати виходжування доношених новонароджених з критичними захворюваннями перинатального періоду. Анікін І.О., Варинський Б.О., Стрижак Л.С., Сергєєва Л.Н., Снісар В.І. *Вивчали результати впливу підвищеного споживання протеїнів та L-карнітину в програмі харчування доношених новонароджених із захворюваннями перинатального періоду на результати фізичного розвитку та на показники лікування в стаціонарі. Метою роботи було вивчення кореляцій між короткотривалим більшим споживанням білка та карнітину доношеними новонародженими і результатами фізичного розвитку дітей, тривалістю госпітального виходжування. Досліджено показники життя 59 доношених дітей, у рандомізованому контрольованому дослідженні, у період з 2017 до 2020 року. Основним критичним захворюванням перинатального періоду в дітей обох груп виявлено гіпоксично-ішемічну енцефалопатію помірного ступеня – 86,7% та 86,2%, без статистично значущої різниці. Група (n=30) отримувала харчування молоком матері (СХ), друга група (n=29) отримувала аналогічне харчування з фортифікацією білковою добавкою (ГЗ) та дотацію L-карнітину протягом перебування в лікарні. На початку і в кінці лікування вивчали фізичний розвиток дітей та досліджували кореляційні зв'язки між отриманими даними. Немовлята обох груп не відрізнялися за характеристиками на початку дослідження. Пропорції ваги немовлят відповідали межам 50% перцентилю. Група підвищеного споживання білка та карнітину демонструвала кращі показники фізичного розвитку малюків, швидше відновлювала масу тіла. Маса тіла дітей групи ГЗ становила 3966,9±439,1 г порівняно з групою СХ 3554,6±452,3 г, при p=0,003. Показник збільшення довжини тіла в ГЗ вдвічі перевищував показник групи СХ. Споживання більшої дози білка супроводжувалось меншим часом перебування у відділенні інтенсивної терапії – 10,0 (8,0;12,0) днів проти 12,0 (11,0;16,0) днів, при U=235,0; p=0,002; раніше виписувались зі стаціонару – 21,0 (19,0; 27,0) день проти 26,5 (22,0; 31,0) днів, при U=267,0, p=0,01. Дотація карнітину в групі ГЗ приводила до підвищення рівня вільного карнітину в останніх зразках плазми крові перед випискою дітей додому. Дослідження кореляцій виявило позитивний кореляційний зв'язок між споживанням повної дози протеїнів та загальним збільшенням зросту (R=0,3, p<0,05), збільшенням маси тіла (R=0,3, p<0,05). Негативна кореляція виявлена між рівнем протеїну та тривалістю лікування в стаціонарі (R= -0,3, p<0,05). Рівень вільного карнітину позитивно впливав на збільшення довжини тіла – (R=0,51, p<0,05), щоденне збільшенням ваги (R=0,3, p<0,05). Погане збільшенням довжини тіла асоціювалася з більшою тривалістю респіраторної підтримки: кореляція мала зворотній напрямок R= -0,4, p<0,05. Удосконалення харчових стратегій має значні перспективи щодо покращення виходжування доношених дітей з критичними захворюваннями перинатального періоду.*

Newborn children, in a certain number, are prone to the influence of perinatal factors: infections, hypoxia, lung disorders, etc. Critical diseases of the perinatal period affect the nutritional capacity of newborns, with a direct impact on the physical development in the population, which should be comparable with healthy ones [1]. A limited number of publications is devoted to the problem and the search for its solution in full-term babies, who are less affected by the above-mentioned factors [2].

Growth retardation is caused, firstly, by malnutrition and the inability to consume enough macronutrients. Secondarily, by disorders of intracellular insulin signaling, a decrease in the level of mitochondrial efficiency, and a defective glucose uptake during a critical disease [3]. Definite norms of nutrient and energy consumption are also recommended for full-term babies who need intensive care due to protein catabolism and the need for additional energy to overcome diseases [4].

Parenteral nutrition can help prevent nutritional deficiency in term infants, but the risks of this intervention, with possible negative consequences, have been proven by a recent multicenter study, so improving the strategy of enteral nutrition is urgent [5]. In a cohort of preterm infants, the deficiency of proteins necessary for growth was solved with the help of "formulas" for nutrition and by enriching breast milk with fortifiers [6, 7]. In the work of V. Koletzko, with a large number of observations, there was studied the increased consumption of protein by full-term babies during the year. Assessment of height and body composition at the age of 6 years showed a 2.6-fold reduction in the odds of obesity in a group of children on conventional feeding, indicating the risks of consuming a large amount of proteins [8]. However, the short-term consumption of an increased amount of proteins and the possible results of such a strategy have hardly been studied [4].

Hypotheses of the impact of L-carnitine supplementation on improving the development care of newborns in critical conditions are another subject of interest for nutritionists. Recently, there have been data on a positive correlation between carnitine consumption and physical development of preterm babies [9]. Almost no studies have been conducted in term infants who required intensive care.

Thus, the purpose of the work was to study the correlations between short-term higher consumption of protein and carnitine by full-term newborns and the results of their physical development, the duration of hospital development care.

MATERIALS AND METHODS OF RESEARCH

We proposed the hypothesis that the early appointment of a statistically greater amount of protein (compared to the level of the usual supplement to full-term babies in the intensive care program) and the addition of L-carnitine to the nutrition protocol will improve the indicators of the physical development of

babies. The minimum and maximum levels of protein supplementation for newborns with critical diseases will not extend existing recommendations [4].

The study participants were treated in the Neonatal Intensive Care Unit (NICU) of the Zaporizhzhia Regional Clinical Children's Hospital. NICU is the clinical base of the Zaporizhzhia State Medical and Pharmaceutical University, which provides tertiary care to babies delivered from health care facilities of the Zaporizhzhia region and the city of Zaporizhzhia of the second level of care.

A prospective, randomized, controlled study was conducted, which involved babies born in the period of gestation from 37 to 41 weeks. In the period from 2018 to 2020, 59 babies were selected, those evacuated from maternity homes and hospitals in critical condition. The main criterion for inclusion in the study was the need for prolonged artificial ventilation of the lungs for more than 72 hours in connection with critical diseases of the perinatal period. Assistance was provided in accordance with the Order of the Ministry of Health of Ukraine dated March 28, 2014. No. 225 (Unified clinical protocol "Initial, resuscitation and post-resuscitation care for newborns in Ukraine").

Cases of babies who are too small and too large for gestational age (according to the nomograms of physical development of fetuses Fenton 2013 [10]), babies with congenital malformations that required surgical treatment, and those ones with congenital metabolic disorders, chromosomal abnormalities, and terminal stages of liver disease were excluded from the study. Thus, at the examination stage, 63 babies were included, but later 4 children were excluded from the study in connection with a congenital heart defect with surgical correction (1), the development of terminal multiple organ failure (1), two children, according to anthropometric measurements were classified as large in relation to gestation period (Fig. 1).

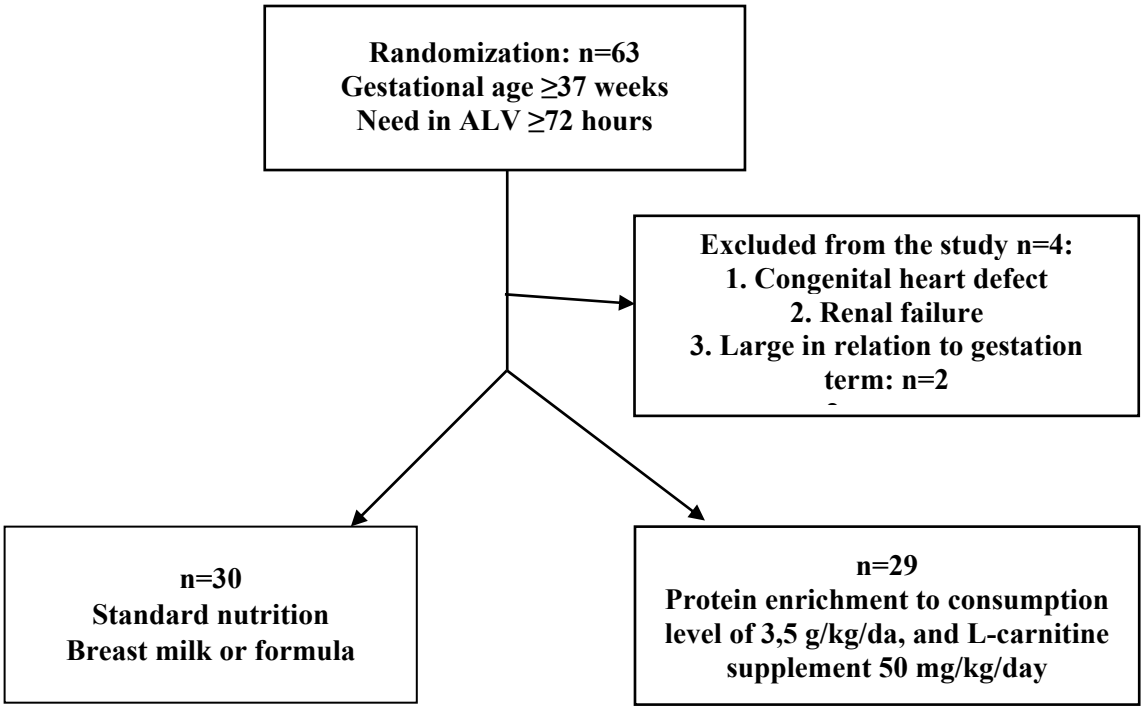

Fig. 1. Study design

Using randomization, babies were divided into 2 groups. The method of random numbers generated in the Statistica program was used. The group of standard nutrition includes 30 (50%) babies who received mainly breast milk. This group was consideredation a control one and received a nutrient supplement according to existing recommendations for newborns who need intensive care. "Blinding" was not performed, parents received full information about the used feeding strategies [4]. At the stage of initial assistance, babies received tube feeding, when swallowing was restored, during the recovery period, they were breast-fed or on bottle feeding. Feeding was increased daily gradually, based on signs of food tolerance.

In the fortification group (29 babies), protein supplementation was used, up to the maximum consumption level of 3.5 g/kg/day, which was carried out using a protein fortifier, which is casein hydrolyzate. The babies received glucose parenterally, with a metabolic rate of consumption from 4 to 6 mg/kg/min, to ensure adequate fluid volume until full enteral nutrition was received, allowing caloric intake at the

basal metabolic rate. The total volume of fluid reached the level of physiological need for the postnatal age. Enrichment was started at a tolerated volume of approximately 80-90 ml/kg/day. The fortifier was calculated daily by adding the required amount into milk or formula for feeding. Averaged data on the protein content in the breast milk of women who gave birth at term and the protein content, according to the instructions in the case of formula feeding, were used for the calculation [11]. According to the protocol, the daily amount of the fortifier was evenly distributed in 4 portions during self-swallowing and in all portions during tube feeding. In the fortification group, the introduction of L-carnitine preparations was also used to prevent the accumulation of deficiency of the substance, in a daily dose of 50 mg/kg/day until discharge from the hospital, after which the administration was stopped. Until a baby received a sufficient volume of enteral nutrition, L-carnitine was administered in the form of an infusion, adding the daily dose to the prepared mixture of liquid and electrolytes, which was administered during the day at a uniform rate. Enteral carnitine syrup was administered when the volume of nutrition reached 90-100 ml/kg/day. The daily dose was administered in three doses, adding to the formula for nutrition or breast milk.

Anthropometric assessment of physical development was carried out on the day of birth and then weekly, or on the day of discharge from the hospital. Measurements of the main anthropometric measures (body weight, head circumference, body length) were used, according to WHO recommendations [12]. Measurements were carried out twice, by two specialists, independently of each other. Body mass was measured with an accuracy of 5 g on calibrated electronic scales. If the difference between the two measurements exceeded 50 g in weight, 0.7 cm in length, and 0.5 cm in head circumference, then both specialists repeated the measurements.

The obtained data were entered into the protocol, comparing them with the nomograms of physical development of Fenton (2013) with further comparative analysis between groups [10]. In addition, a comprehensive assessment of the somatic and neurological status of the babies was carried out. The biochemical profile of newborns was obtained weekly, which was required by the general clinical examination protocol. Blood samples of babies reached 0.5 ml, but did not exceed 1.0 ml. The safe tolerance to the protein load was monitored by the level of phenylalanine, urea and creatinine in the blood plasma. Free plasma carnitine (FC) and phenylalanine levels were studied at the beginning of the examination and at the last week of treatment of babies using the method of liquid chromatography-mass spectrometry (LC-MS Agilent 1260 Infinity HPLC System, USA), using standard substances of the Sigma-Aldrich company.

The research protocol was agreed and approved by the regional Commission on Bioethics of the Zaporizhzhia State Medical and Pharmaceutical University of the Ministry of Health of Ukraine, according to the approved regulation (Protocol No. 4 dated May 28, 2018). The research was carried out in compliance with moral and ethical standards in accordance with the rules of the IGH/GCP, the Declaration of Helsinki (1964 with additions in 1975, 1983, 1989, 1996, 2000), the Council of Europe Convention on Human Rights and Biomedicine, and the legislation of Ukraine. Informed written consent was obtained from the patients' parents before the start of the study. All parents had the opportunity to receive information about the progress of the research and the obtained results.

Data were tested for normality of distribution using the Shapiro-Wilk test. In the text and tables, the data are presented as M±SD (arithmetic mean ± standard deviation) in the case of a normal distribution of the trait, Me (Q1; Q3) (median of the sample with an indication of the interquartile range as the upper (75%) and lower (25%) quartiles – in a non-normal distribution. Categorical variables are presented as absolute number of cases (n) in a group and frequency as a percentage (%).

All statistical analyzes were performed using Statistica 13.0 software, TIBCO Software Inc. (license number JPZ804I382130ARCN10-J) and Microsoft Excel 2013 (license number 00331-10000-00001-AA404). Determining the probability of the difference in the absolute values of the mean values was carried out using non-parametric methods of statistical analysis: the Mann-Whitney test (U) for unrelated groups and the Wilcoxon test (T) for related groups. Spearman (ρ) non-parametric correlation methods were used. The significance of the relationship between parameters was determined according to Cheddoke: high – when ρ exceeded 0.7, noticeable – 0.5-0.7, moderate – 0.3-0.5, weak – 0.1-0.3. Statistical differences were considered reliable at $p<0.05$ [20].

RESULTS AND DISCUSSION

A total of 59 newborns were studied, of which 30 were included in the standard nutrition group (SN) and 29 were included in the fortification group (FG). Babies in the fortification group, by design, consumed more protein and carnitine. Newborns did not differ in terms of gestational age and physical development characteristics. Boys predominated in each group, respectively 70 and 62%, p=0.52. The main perinatal condition was hypoxic-ischemic

encephalopathy at birth, which was diagnosed according to the Sarnat and Thompson scale. Caesarean section was required with a negligible frequency of intervention, which did not differ: 16.67% in the SN group and 20.69% in the FG group, p=0.69. As expected, the newborns were comparable with respect to other diseases of the perinatal period. Newborns were breast-fed, respectively 86% in the SN group and 90% in the FG group, p=0.64. Clinical characteristics of groups are given in Table 1.

Table 1

Clinical characteristics of population under study (M±m and Me[LQ; UQ])

Characteristics, units of measure	Standard nutrition (n=30)	Fortification group (n=29)	p-level
Term of gestation, weeks	38.7±1.26	39.00±1.13	0.39
Body mass at birth, g	3265.13±366.60	3452.24±413.58	0.07
Body length, cm	52.17±2.32	53.16±2.13	0.09
Head circumference, cm	34.27±1.17	34.69±1.01	0.15
Boys, n (%)	21.00 (70.00%)	18.00 (62.07%)	0.52
Apgar score at first minute, points	7 (5; 7)	6 (5; 7)	0.48
Apgar score at fifth minute, points	7 (7; 8)	7 (6; 8)	0.25
Cesarian section, n (%)	5.00 (16.67%)	6.00 (20.69%)	0.69
Hypoxic-ischemic encephalopathy, n (%)	26.00 (86.67%)	25.00 (86.21%)	0.96
Neonatal sepsis, n (%)	1.00 (3.33%)	2.00 (6.90%)	0.53
Meconium aspiration, n (%)	3.00 (10.00%)	2.00 (6.90%)	0.67

Note. p-level is a statistically significant difference.

Body length at birth was proportionally greater relative to weight, with both cohorts showing values within the <90% and >50% percentiles. The indicators of mass and head circumference, at the first measurement in infants were within the 50% percentile.

Satisfactory tolerance to food load made it possible to achieve appropriate amounts of food. Already at the end of the first week of life, respectively, the newborns in the groups assimilated: FG – 141.81±20.18 ml/kg/day and
SN – 131.87±30.63 ml/kg/day, p=0.15;
on day 14: FG – 163.43±17.46 ml/kg/day and SN – 156.12±13.25 ml/kg/day, p=0.07. Food tolerance indicated the beginning of the "recovery" phase of a critical illness. Rapid achievement of the full volume of enteral nutrition made it possible to carry out protein fortification in the first week of life. The increase in volume was stopped when the consumed amount per day was 150-165 ml/kg. Parenteral nutrition using lipid emulsions and amino acids was not carried out in accordance with modern requirements focusing on patient safety [4] Dynamics of protein consumption in groups is presented in Fig. 2.

In the fortification group, from the 7th day of life, we achieved a protein supplementation at the level of approximately 3.5 g/kg/day. This corresponded to the limits for critically ill full-term babies (2.0-3.5 g/kg/day) who entered a stable phase of "recovery" of critical perinatal diseases, and the total protein dose reached the maximum recommended for consumption, according to ESPGHAN 2021 recommendations [4]. The level of deviation from the average during the entire stage of growth was low, which was achieved thanks to the automatic calculation of the nutrition of babies. Thus, on day 14 and 21, due to fortification, children continued to consume protein of 3.5 (3.4; 3.6) g/kg/day and 3.5 (3.5; 3.5) g/kg/day, respectively, and the level of protein consumed from breast milk or formula was 2.3 (2.3; 2.5) g/kg/day and 2.4 (2.3; 2.6) g/kg/day, respectively.

Protein consumption by babies in standard nutrition was on average 2.35 (2.3; 2.5) g/kg/day and 2.4 (2.3; 2.5) g/kg/day on day 14 and 21, which was also within the guidelines. When comparing the consumption of the total amount of proteins in the stable development care phase, it should be noted that a statistically significant difference was found between the groups: 3.5 (3.4; 3.6) g/kg/day, against 2.35 (2.3; 2.5) g/kg/day, with U=80.00; p=0.0001 on the 14th day of life, and 3.5 (3.5; 3.5) g/kg/day, against 2.4 (2.3; 2.5) g/kg/day, with U=50.00; p=0.0001 on day 21.

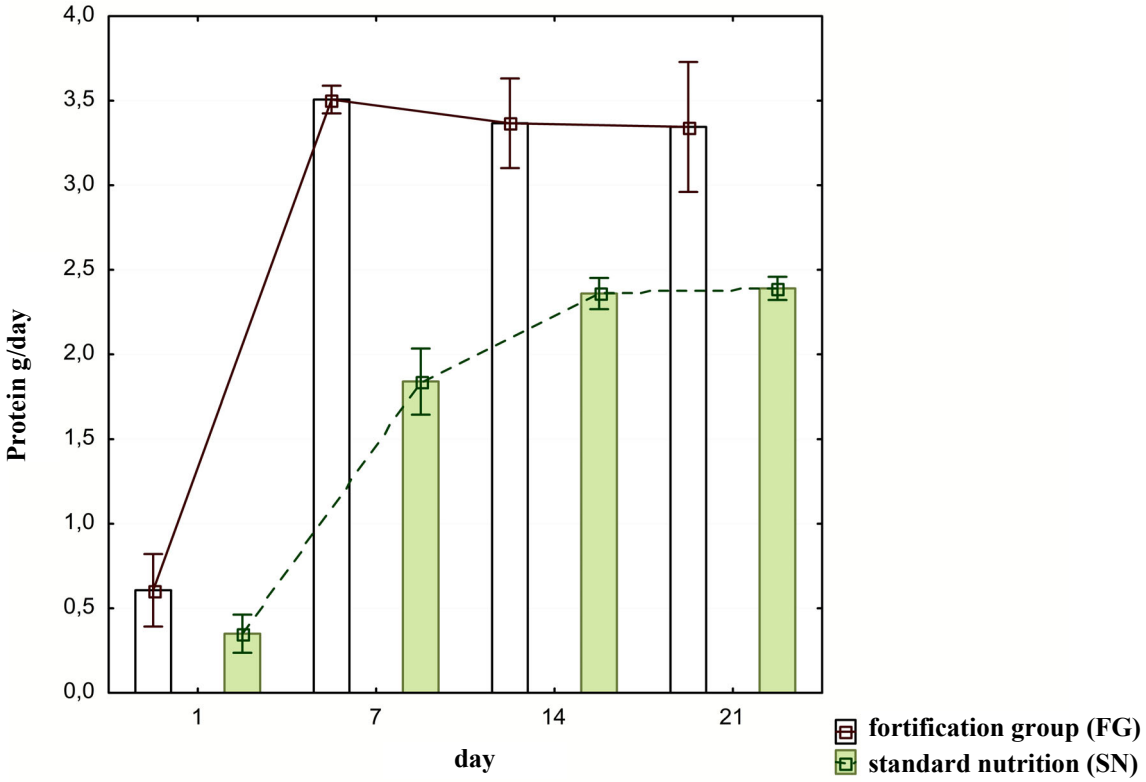

Fig. 2. Dynamica of protein consumption in groups

Carnitine supplementation was controlled by the level of free substance at the beginning and end of the study (Fig. 3). The level of free carnitine increased in newborns of both groups during treatment. In the group of standard nutrition at the beginning, the level of free carnitine was 13.67 (10.08; 18.61) μmol/l, during the development care period it increased due to breast milk supplementation. Before discharge, the level was 24.97 (18.99, 38.85) μmol/l, which was statistically higher than at the beginning (p=0.0003).

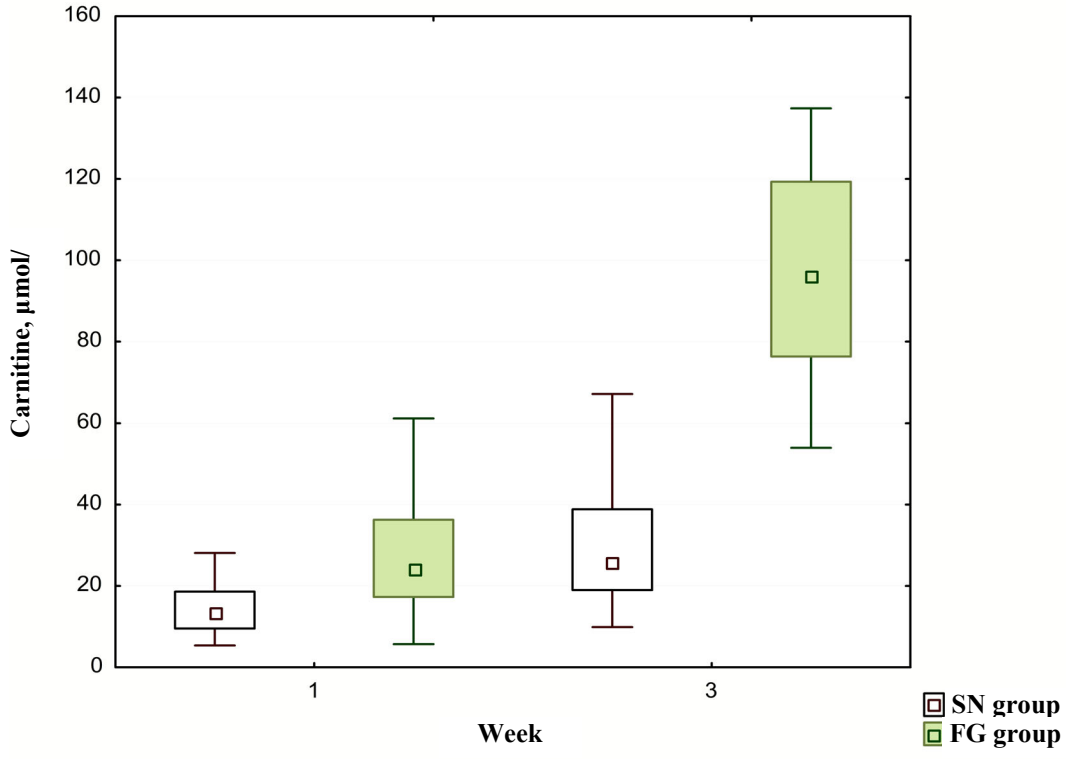

Fig. 3. Dynamics of free carnitine content at the beginning of treatment and at the 3rd week

In the fortification group, additional enrichment with carnitine contributed to the fact that in the last measurements the level of the free substance was on average 96.18 μmol/l (76.33; 119.32), in the first samples in this group it was 24.17 μmol/l (20.22; 36.29), U=35.0000; p=0.0001.

The main criteria for comparing the effectiveness of the nutritional support strategy for newborns are indicators of physical growth and indicators of hospital stay. Focusing on the growth data of newborns regardless of gender (Table 2), it turned out that babies in the SN group initially lost more weight, and its recovery was slower compared to the FG group. Newborns in the FG group regained weight almost twice as early (Table 3). FG babies, regardless of gender, showed a better increase in body weight, length and head circumference from the second week of life. When assessing newborns' physical growth by normative curves, a parallel nature of weight gain and head circumference in FG group was found from the first week of life. This tendency persisted until the moment of discharge from the hospital. The descending nature of the above-mentioned parameters from the moment of birth to the 7th day of life was studied for the newborns of the SN group. But, then the direction of the growth graph changed and acquired an ascending character parallel to the curve of the 50% percentile, similar to the study group, until the moment of discharge from the hospital. On the 28th day of life, most of the newborns in the fortification group were discharged from the hospital, so the comparison of anthropometric growth markers was not significant.

Table 2

Dynamica of physical development of newborns (M±m)

Characteristics, units of measure	Standard nutrition (n=30) #	Fortification group (n=29) #	p-level
Body mass, g (M±m)			
at birth	3265.13±366.60	3452.24±413.58	0.07
day 7	3224.00±419.64	3545.83±405.39	0.004
day14 or on discharge	3406.83±402.79	3764.64±687.73	0.001
day 21, or on discharge†	3554.62±452.28	3966.90±439.08	0.003
Body length, cm (M±m)			
at birth	52.17±2.32	53.16±2.13	0.09
day 7	52.47±2.47	53.81±1.78	0.02
day14 or on discharge	53.00±2.35	55.30±2.79	0.001
day 21, or on discharge†	53.52±2.04	55.83±1.43	0.0001
Head circumference, cm (M±m)			
at birth	34.27±1.17	34.69±1.01	0.14
day 7	34.57±1.13	35.10±1.04	0.06
day14 or on discharge	34.90±1.19	35.77±1.00	0.004
day 21, or on discharge†	35.56±1.41	36.32±1.02	0.05

Notes: p-level – statistically significant difference; # – number of children day 1 to day 14 of observation; † – the number of observations on day 21-26 in the SN group, and n=20 – in the FG group.

The increase in head circumference in both groups changed in the same way, without statistical difference. The curve had an ascending character, parallel to the 50% percentile according to nomograms of newborns's development.

Newborns in FG demonstrated greater daily weight gain and, accordingly, faster recovered the body weight lost at birth (Table 3). In general, among babies who statistically developed better physically, a shorter stay in the intensive care unit and in the hospital was

noted, which was influenced by the shorter duration of artificial lung ventilation (Table 3). Thus, only 7 (24.14%) newborns of the group of increased protein consumption remained under treatment after day 23, and 15 (50%) from the group of standard nutrition remained on therapy. When comparing the average increase in body length, it was found that newborns in the group with higher consumption of protein and carnitine on average grew by 2 cm, which turned out to be almost twice as much as the ones in the standard nutrition group, with a statistically proven difference. There were no fatal cases in the groups, all the newborns were discharged home.

Table 3

Overall results of development care in hospital and NICU (M±m)

Characteristics, units of measure	Standard nutrition (n=30)	Fortification group (n=29)	p-level	U
Day of weight restoration	**10.0(8.0;16.0)**	**5.0(1.0;8.0)**	**0.0002**	**173.00**
Weight gain (g/kg/day)	**18.62(12.5;24.3)**	**24.76(14.2;30.36)**	**0.02**	**263.00**
Length increasing (cm)	**1.00(0.0; 1;00)**	**2.00(1.00;2.00)**	**0.003**	**237.00**
Duration of mechanical ventilation, days	**7.5(5.0;10.0)**	**6.0(4.0;7.0)**	**0.007**	**258.00**
Length of stay jn NICU	**12.0 (11.0;16.0)**	**10.0 (8.0;12.0)**	**0.002**	**235.50**
Length of hospital stay, bed-days	**26.5 (22.0;31.0)**	**21.0 (19.0;27)**	**0.01**	**267.00**

Notes: p-level – statistically significant difference; U – Mann-Whitney test.

The analysis revealed a direct positive correlation between the consumption of a full dose of proteins and the total length increasing (R=0.34, p<0.05). Also, length increasing was positively influenced by a higher level of free carnitine (R=0.51, p<0.05) (Fig. 4). A positive correlation of higher carnitine levels with average daily weight gain was found (R=0.30, p<0.05).

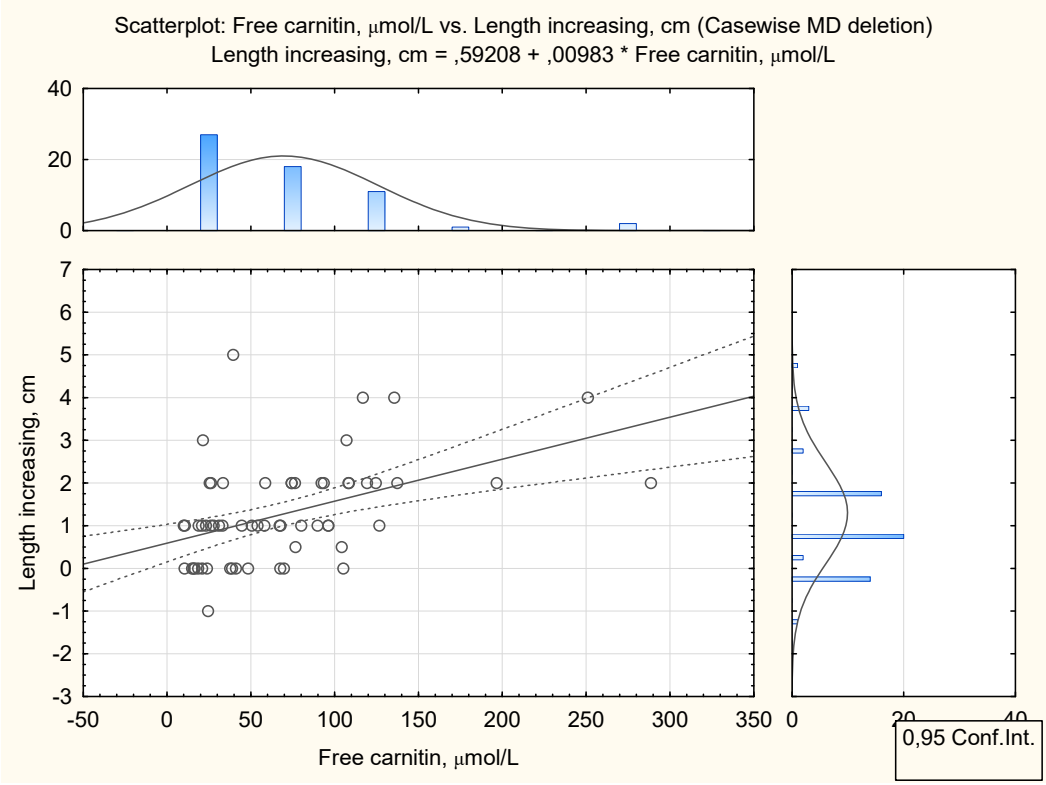

Fig. 4. Impact of free carnitine level on length increasing

Body weight gain in newborns was positively influenced by the dose of proteins at the end of development care (R=0.26, p<0.05), as well as the level of free carnitine in the plasma at the same time (R=0.28, p<0.05). A negative linear correlation was found between the amount of protein consumption and the duration of treatment in the hospital (R= -0.30, p<0.05). All correlations were weak according to the Chaddock scale.

A poor body length increasing was associated with a longer duration of respiratory support: the correlation had an inverse direction R= -0.40, p<0.05. Accordingly, the longer need for respiratory support had a positive correlation with the length of stay in intensive care unit (R=0.84, p<0.05) (Fig. 5) and hospital stay (R=0.58, p<0.05), which yet again indicates a possible relationship of nutritional support with the effectiveness of intensive therapy of critically ill patients of neonatal age.

Also, in our analysis, we did not find evidence of a direct effect of protein consumption on the duration of treatment, including with the use of mechanical ventilation. Instead, the consumption of carnitine, and the corresponding increase in the level of free carnitine showed a negative correlation relationship with the above indicators. Thus, the correlation with the length of stay in the intensive care unit was R= -0.35, p<0.05, (Fig. 6), and with the total hospital stay – R= -0.26, p<0.05.

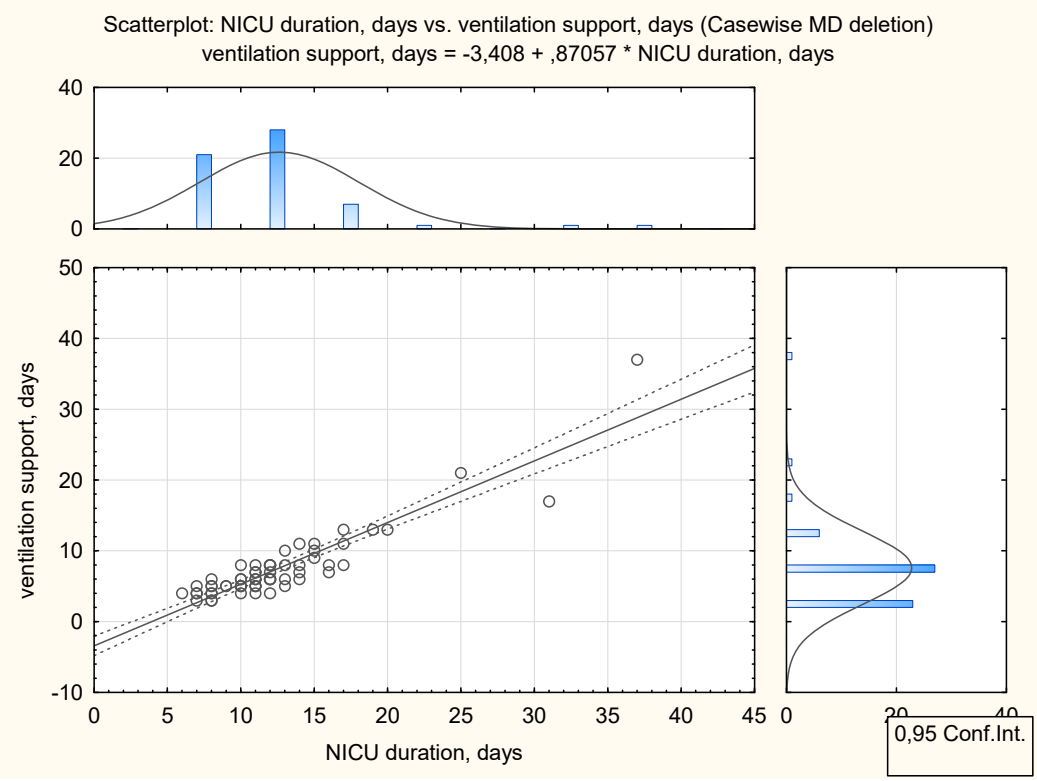

Fig. 5. Relationship of respiratory support duration with duration of staying in NICU

In our study, children of both groups had limited opportunities for enteral nutrition during the first two weeks, so they did not receive carnitine supplements with mother's milk at the required level. This, accordingly, increased the risks of secondary carnitine deficiency. As a result, in this study we demonstrated that the prophylactic administration of carnitine, in cases where the newborn cannot be fed enterally, helps to prevent the accumulation of deficiency of this substance. Accordingly, this reflects an increase in the level of free carnitine in blood plasma. Higher carnitine intake in full-term infants during the first 3 weeks of life, as well as higher serum carnitine levels, is associated with better postnatal physical growth. In addition, in this work we found that early higher protein supplementation in critically ill full-term newborns also has a positive effect on the recovery and subsequent increase in body weight. The obtained results emphasize the importance of a nutritional support strategy for newborns with severe diseases of the perinatal period, and the importance of carnitine and protein intake for postnatal growth and the impact on the duration of development care in the hospital.

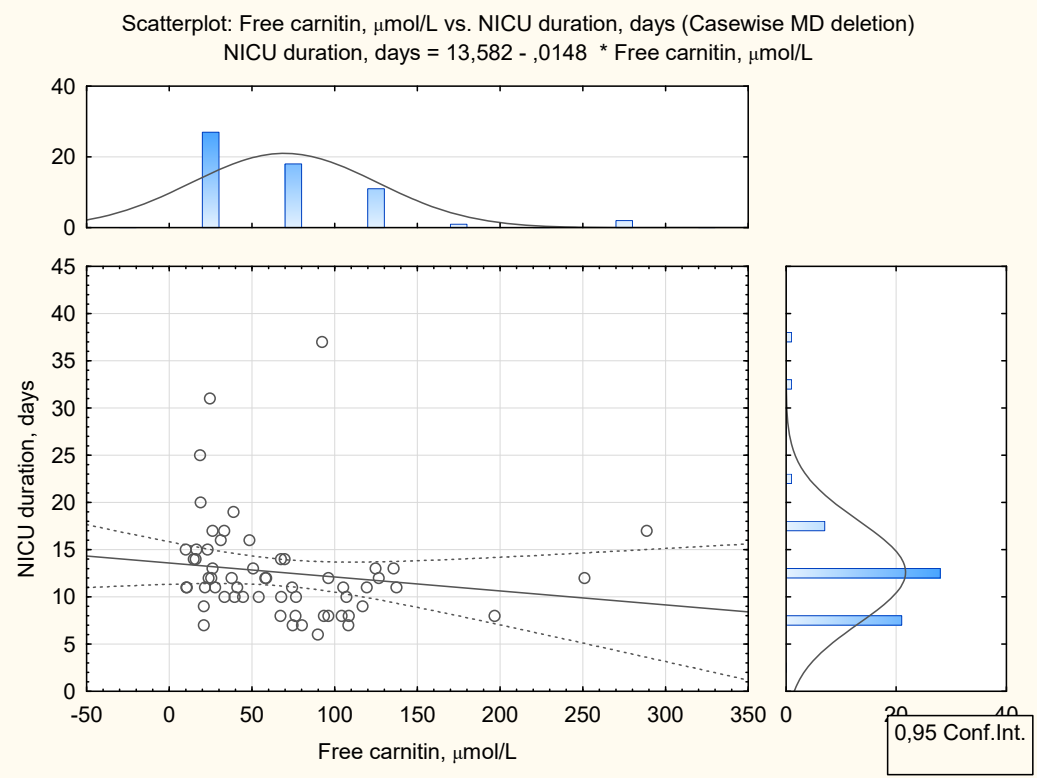

Fig. 6. Relationship of free carnitine level with duration of staying in NICU

Although a large number of studies have been conducted on the study of carnitine insufficiency in children, the reference values for the content of free carnitine in newborns differ. Chace DH. indicates that the normal level of FC in full-term infants reaches 46.41±20.73 μmol/l [13]. However, other authors indicate the limit levels of free carnitine at the level of 20-26 μmol/l, which are capable of variability during the first month of life. In our study, only additional early supplementation of carnitine made it possible to exceed the concentration of the substance demonstrated by Chace DH.

In the observational study, Cam H. proved that hypoxic-ischemic encephalopathy is a risk factor for secondary carnitine insufficiency. Thus, children with HIE had a lower level of carnitine compared to healthy children, which reached 13.2±6.8 μmol/l. In our study of a cohort of full-term children with HIE, we obtained similar levels of free carnitine concentrations, and demonstrated the achievement of a higher level in blood plasma with early external supplementation at a dose of 50 mg/kg/day [14]. Most studies on the use of carnitine supplementation in preterm infants are also conflicting. Several studies of supplementation have shown that the clinical effect in terms of growth or hospital stay was moderate, despite higher FC level after parenteral carnitine administration. In a prospective, placebo-controlled study of preterm infants with a very low birth weight, who received carnitine supplementation initially at a dose of 15 mg/kg/day intravenously and after the establishment of total enteral nutrition at 100 mg/kg/day orally in 4 doses, there was no revealing that this strategy improves physical development [15]. In full-term newborns with diseases that required treatment in the NICU, carnitine supplementation and its effects have hardly been studied. However, previous studies examining the relationship between serum carnitine concentration and postnatal growth of preterm infants, depending on the levels of acylcarnitine metabolites, have established positive linear correlations. It has been found that growth retardation after birth is associated with postnatal deficiency of long-chain acylcarnitine (eg, C18:1 and C18:2) with corresponding growth in preterm infants. In this study, acylcarnitine (C2 and C3) concentrations were associated with change in weight Z-score in a linear regression model [16].

Another study in a group of preterm babies demonstrated the existence of a direct correlation between the normal content of carnitine in the blood plasma and the Z-scores of the growth, as well as the effect on the increase of almost all parts of the brain. Linear regression models proved the direct influence of the level of FC on the achieved results [9]. In our work, we also obtained correlations between physical growth and the level of carnitine in blood plasma. Improved physical development contributed, in turn, to faster recovery and discharge of children.

In this study, we found weak correlations between protein intake and weight gain in children, as well as a weak effect on length of stay in the intensive care unit. However, the practice of higher protein intake continues to demonstrate better growth and neurodevelopmental outcomes in cohorts of children with low birth weight. A recent prospective study conducted in eight neonatal intensive care units in New Zealand and Australia examined the effects of macronutrient intake from birth to 4 weeks of postnatal age. Measurements of weight, length, and head circumference from birth to 36 weeks revealed higher median z-scores: for weight -0.48 (-1.09, 0.05); length -1.16 (-1.86, -0.43), head circumference -0.82 (-1.51, -0.19). Changes in z-score were correlated with protein intake. Each 1g/kg/day of total protein intake in the 2nd week of life was associated with a 0.26 increase in head circumference for z-score up to 36 weeks of postmenstrual age [17]. In our study, we avoided parenteral nutrition (PN) in both groups of children. The negative consequences of early PN in full-term newborns have been demonstrated recently in the PEPaNIC multicenter study [18]. In order to compensate for the cumulative deficit of nutrients and energy, we tried to increase the volume of enteral nutrition more quickly and to study the results of increased protein consumption. The obtained data revealed a correlation between protein intake and body length increasing.

The results of this work demonstrate the advantages of the proposed nutrition strategy for children with perinatal diseases, but they have limitations due to the lack of accurate data on protein intake during breastfeeding. Determining the protein content in specific women is not provided by the design, so better results could be obtained by measuring the macronutrient content of each woman's breast milk and individual fortification. To obtain more reliable results, we used the available literature that contains data on the composition of human milk [11, 19]. Also, the issue of the dose of additional carnitine intake in children with limited nutritional opportunities is not resolved and controversial.

CONCLUSIONS

1. Consuming more protein versus a statistically lower dose, within the recommendations for critically ill full-term babies, promotes better physical development and is accompanied by a shorter duration of hospital treatment. In our analysis, we did not find evidence of a direct effect of protein consumption on the duration of treatment, including with the use of artificial lung ventilation.
2. Additional carnitine supplementation given to full-term babies has a positive correlation with length increasing and total body weight gain. Accordingly, there is a negative correlation between the level of free carnitine in blood plasma and the duration of the need for respiratory support, the term of hospital discharge.
3. In full-term newborns with critical perinatal diseases, nutritional strategies have significant prospects for improving development care of this group, in view of the revealed inverse correlations between growth and duration of treatment.

Prospects for further research: to further study the possible effects of a combination of nutritional support factors on physical development of newborns, further research on the short-term and long-term effects of nutritional strategies would be appropriate.

Contributors:

Anikin I.O. – supervision, investigation, resources, data curation, methodology;

Varynskyi B.O. – investigation, resources;

Stryzhak L.S. – resources, data curation;

Serhieieva L.N. – formal analysis, writing – original draft, visualization;

Snisar V.I. – validation.

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Conflict of interest. The authors declare no conflict of interest.

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