EVALUATION OF THE EFFECTIVENESS OF NUTRITIVE THERAPY IN THE TREATMENT OF SEPSIS IN CHILDREN

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Abstract*. This study seeks to assess the effectiveness of nutritional intervention involving glutamine in pediatric patients afflicted with sepsis. Sepsis, marked by a systemic inflammatory reaction to infection, is a grave condition that continues to pose significant risks to children's health. The article outlines an investigation into the efficiency and safety of utilizing glutamine in managing sepsis among pediatric populations. It examines findings from clinical trials exploring the impact of glutamine on various clinical and laboratory indicators, as well as treatment outcomes, in children diagnosed with sepsis.*

The results of the analysis allow us to conclude the potential efficacy and safety of the use of glutamine in the complex therapy of sepsis in children. This article may serve as a basis for the development of more effective nutritional support strategies in children with sepsis using glutamine.

Keywords*: nutritional deficiency, children, sepsis, nutrients, glutamine.*

Introduction. Nutritional inadequacy among children with sepsis remains a significant public health challenge, particularly in less developed nations. This issue contributes significantly to illness and death rates among children below the age of five. Given that the pediatric ICU population is extremely heterogeneous in terms of severity of pathology, nutritional status, age, comorbidities, and other criteria, an individualized approach to nutritional therapy is needed to improve clinical outcomes. According to researchers' estimates, the annual incidence of sepsis in the pediatric population is 4.2 million cases, including 3 million cases in newborn children. 3 out of 10 deaths from neonatal sepsis are suspected to be caused by antimicrobial-resistant pathogens [1,2]. Early diagnosis and treatment of sepsis are highly complicated due to its pathogenesis, marked individual variability of clinical and laboratory manifestations, and immune status. The primary catalyst behind the diverse clinical presentations of sepsis is the body's intrinsic response aimed at containing the infection. However, when this endogenous response becomes unmanageable, it often leads to organ dysfunction and protein-energy malnutrition. These factors stand as the primary contributors to mortality among patients in the Pediatric Intensive Care Unit (PICU) [9]. «Nutritional therapy, an essential component of intensive care for sepsis/septic shock, aims to prevent the multi-inflammatory syndrome and organ-systemic damage, increase immune protection, and reduce mortality» [25].

By nutritional deficiency we mean insufficient nutrient intake or nutrient absorption, resulting in impaired normal growth and development in children. This deficiency can manifest itself in various ways, from delayed physical development to decreased immunity and increased risk of infectious diseases. The problem of nutritional correction of hypermetabolism-hypercatabolism syndrome in critical conditions in children is reflected in multicenter reviews [10, 11]. Currently, there is a growing interest in the study and management of nutritional deficiency in children, especially in the context of their morbidity and mortality in infectious diseases such

as sepsis. «Multicomponent intensive therapy for sepsis included detoxification therapy, respiratory support (if necessary, mechanical ventilation), correction of water-electrolyte, hemodynamic disorders, inotropic support, nutritional and immunotherapy»[24]. Recommendations for nutritional therapy in critically ill children from 1 month to 18 years of age are given in the ASPEN/SCCM (2017) guidelines [1,2,3,23], which reflect the analysis of about 2000 clinical trials and cohort studies (best practices for nutritional support in pediatrics). The gastrointestinal tract (GI) tract, as an organ with intensive metabolic processes, is among the first to be affected, as 50-80% of intestinal nutrition is provided by intracavitary substrates necessary for the growth and regeneration of its cellular structures. Recent studies have shown that the main link in the pathogenesis of multiorgan dysfunction syndrome development in critical conditions is intestinal failure syndrome (IFS) [8, 9]. Suppression of GI motility in combination with disorders of cavity digestion, and morpho-circulatory changes in the intestinal wall contribute to bacterial translocation into the systemic circulation [13,14]. Nutritional correction using glutamine is one of the important directions in modern medicine, especially in the context of the treatment of various diseases and conditions associated with nutritional status disorders and damage to the mucosal membranes of the gastrointestinal tract. In recent decades, glutamine has attracted increasing attention from the medical community due to its potential effect in maintaining and restoring the integrity of the gastrointestinal mucosal membranes, as well as in improving immunity and regulating metabolic processes. Glutamine, as an amino acid important for cellular metabolism, plays a key role in maintaining immune system function, protein synthesis, and providing energy to cells. Published work in the last decade has demonstrated the safety of glutamine in critical care pediatric parenteral nutrition regimens and the absence of serious complications [10,12]. This is particularly important in the context of diseases such as acute infections, trauma, cancer, and septicemia, which are often accompanied by malnutrition and deterioration of the patient's condition.

Materials and Methods: A prospective, non-randomized study was undertaken involving patients admitted to the clinic of Tashkent Pediatric Medical Institute (TashPMI) and NDMC with sepsis of different etiology. In the period from January 2022 to December 2023.

Inclusion criteria in the study were - signs of organ dysfunction pSOFA ≥3 points, Procalcitonin >0.5 ng/ml, Age - children under 18 years, no contraindications for nutritional support, availability of the necessary scope of examination, informed consent of parents or legal representatives of the child to participate in the study. Exclusion criteria for participation in the study included refusal by the patient or their relatives to participate, patients in a state of shock, individuals with inoperable malignant tumors, decompensated heart failure, fibrinolytic bleeding, and intolerance to components of parenteral or enteral nutrition.

Group 1 (n=38) consisted of patients with severe surgical sepsis whose parenteral nutrition included proteins, fats, carbohydrates, and pharmaconutrient glutamine in the amount of 0.3-0.4 g/kg body weight (20% solution of ‘Imuna’ for 7 days). During this stage, the energy supply averaged 28.78±1.87 Kcal per kilogram of body weight. Enteral nutrition was typically administered for an average duration of 3.75±0.68 days.

Group 2 (comparative) consisted of 42 patients diagnosed with severe surgical sepsis, who received parenteral nutrition without the inclusion of the pharmaconutrient glutamine. The initial energy supply for this group was 29.44±2.46 Kcal per kilogram per day. Enteral nutrition commenced after an average of 4.53±0.85 days from the initiation of treatment.

Initially, patients from both groups were similar in terms of sex and age distribution, severity of the condition as assessed by SAPS and pSOFA scales, body mass index, extent of nutritional deficiency, and protein-energy supply. The degree of protein-energy malnutrition (PEM) was evaluated based on anthropometric measurements and laboratory findings. The anthropometric approach includes measurements of the child's weight and height, as well as the circumference of the upper arm and the thickness of the skin-fat fold over the triceps, determined by caliperometry.

Anthropometric assessment:

- Child's weight/height: Measuring the weight/height ratio is an important parameter. A low ratio may indicate potential nutritional and growth problems.

- Shoulder circumference: Measuring shoulder circumference can provide information about muscle mass and nutritional status.

- Skin-fat thickness over the triceps: Assessment of subcutaneous fat thickness using calipers can provide insight into fat mass and changes in nutritional status.

Laboratory Evaluation:

- Albumin content: Blood albumin levels can serve as an indicator of protein status and can be evaluated to determine the presence of protein-energy deficiency.

- Absolute Blood Lymphocyte Count: Lymphocytes are important cells of the immune system and their absolute count can indicate immune status and overall nutritional status.

- Total Protein: Estimating the total amount of protein in the blood can provide information about the overall nutritional status of the body.

These parameters together help to make a comprehensive assessment of PEM and determine the necessary corrective measures in terms of nutrition and treatment. All comprehensive diagnostic methods were prescribed and performed on admission to the shock room or PICU. On the first day all patients were diagnosed with sepsis and PEM and early adequate correction of sepsis and PEM was initiated.

The sequence of actions in PEM

1 Determination of the cause of PEM

2. Establishing the extent of the deficit.

3 Assess and determine the child's essential nutrient and kilocalorie requirements depending on the degree of protein-energy deficiency (PED). In the setting of sepsis and the development of PED, the body's energy and nutrient requirements can change significantly.

4. Calculation of actual nutrient requirements.

- Protein requirement was calculated according to ESPEN recommendations and Shofield formula, in addition, the efficiency of nitrogen excretion with urine was estimated.

- carbohydrates accounted for 50-70% of non-protein calories.

- fats were 30-50 % of non-protein calories.

5. Individual correction of the qualitative and quantitative composition of the diet, taking into account the specifics of the pathology, the results obtained and the functional capabilities of the child. To maintain morpho-functional integrity of the intestinal mucosa and to reduce the level of bacterial translocation, as well as to stimulate the immune function of the intestinal wall in the program of mixed parenteral-enteral nutrition (PEP), the main group was administered parenteral mixtures of 20% glutamine solution (Imun) at a rate of 2 ml/kg/s for 5 days, with an infusion rate of 0.5 ml/min for the first two hours.

6. Systematic monitoring of the child's needs in basic nutrients and kilocalories by the dynamics of body weight

Patients were transferred from the intensive care unit to specialized departments based on individual decisions, taking into account the comprehensive improvement in their condition, reduction of leukocytosis and procalcitonin level less than 0.5 ng/ml, as well as regression of the sum of pSOFA score ≤ 3.

Results and their discussion: A distinctive feature of metabolism in patients with sepsis was noted not only increased energy consumption but also the inability to assimilate standard nutrients (glycogen, fatty acids, etc.) with preferential utilization of own protein. The heightened degradation of endogenous proteins in patients during the post-aggressive period was indicated by notable hypo- and dysproteinemia. The indices of total protein and albumin on the background of combined nutrition in the main group had a positive trend. In the main group, a statistically significant increase in total protein was observed on day 14, albumin on days 10 and 14 of the study (Table 1). Nevertheless, these laboratory criteria did not reach the lower limit of the norm even after 2 weeks of intensive therapy. However, their changes made it possible to record the transition of malnutrition from moderate to mild degree in the predominant part of patients.

Table 1. Dynamics of protein metabolism parameters

Indicators (norm)	Group 1 (‘Imun’)					Group 2 (Comparative)				
	Study days									
	1	5	7	10	14	1	5	7	10	14
Total protein (66-81 g/l)	51,34 ± 2,16	60,0 ± 2,2	61,31 ± 2,46	62,4 ± 2,23	64,0 ± 2,66	53,29 ± 1,88	58,39 ± 1,33	60,0 ± 1,65	60,5 ± 2,34	62,0 ± 1,59
Albumin (39-49 g/l)	27,02 ± 0,83	30,99 ± 1,34	33,28 ± 1,73	34,59 ± 1,49	34,94 ± 1,34	27,58 ± 1,03	29,89 ± 1,08	30,27 ± 1,2	30,96 ± 1,65	33,66 ± 1,52

According to the study findings, with the addition of 'Imun' at a dosage of 2.0 ml/kg/day to the nutritional support regimen, there was an earlier observed trend toward reducing the severity of catabolism compared to the control group. Glutamine infusion was continued for 7 days. By this time, an increase in the level of total protein to 61.31 ± 2.46 g/l and albumin to 33.28 ± 1.73 g/l was noted (Table 1). In the control group, total protein was 60.0 ± 1.65 g/l and albumin was 30.27 ± 1.2 g/l. It is noteworthy that the rise in albumin levels in the group receiving glutamine was statistically significant as early as day 5, whereas in the comparison group, this increase was observed only by day 14. The dynamics of total protein in both groups had a significant difference compared to the initial data.

Initially expressed lymphocytopenia in both groups corresponded to the average degree of severity of malnutrition (Table 2). Already by the 5th day of combined nutrition, there was a tendency to increase the level of absolute number of lymphocytes in the main and comparative groups. The subsequent increase of the index was also noted, the rate of increase being most pronounced in the main group. Nevertheless, the values of ANL by 14 days remained still within the framework of nutritional deficiency of mild degree in both groups.

Table 2. Dynamics of nutritional support lymphocyte levels (M ± m).

Indicators (norm)	main					Control				
	Study days									
	1	5	7	10	14	1	5	7	10	14
Lymphocytes (19-37%)	12,97 ± 1,66	13,72 ± 1,34	17,81 ± 1,62	19,5 ± 2,23	21,42 ± 2,84	12,03 ± 1,49	16,07 ± 1,48	16,68 ± 1,85	22,17 ± 1,74	17,86 ± 1,66
Absolute number lymphocytes (>1,8 thousand))	1,4 ± 0,20	1,53 ± 0,20	1, 6 ± 0,15	1,64 ± 0,20	1,66 ± 0,16	1,44 ± 0,16	1,53 ± 0,14	1,58 ± 1,17	1,6 ± 0,15	1,55 ± 0,16

* $p < 0.05$ compared with baseline data.

The data obtained were subjected to statistical analysis using programs developed within the EXCEL package on a Pentium-4 personal computer. Statistical functions were utilized to calculate the arithmetic mean (M), standard deviation (σ), standard error (m), relative values (frequency %), Student's t-test, and probability of error (P). Differences in mean values were deemed significant at a significance level of $P<0.05$. The established guidelines for statistical processing of clinical and functional examination results were strictly adhered to.

Conclusions: The study of nutritional status and frequency of intestinal failure syndrome development makes it possible to predict the course of sepsis in children. Complex clinical and biochemical examination of children with sepsis revealed a reliable pronounced degree of protein-energy deficiency, which required timely and adequate nutritional support. The obtained results of complex laboratory examination recorded progressive protein-energy deficiency in septic patients with the absence of body weight deficiency. The incorporation of glutamine into the metabolic therapy regimen for patients with sepsis results in the normalization of protein metabolism parameters. Specifically, the levels of total protein increased by 19.4% and albumin by 23.13% after 7 days of glutamine administration. Therefore, the integration of glutamine into the therapeutic nutrition program proved to be a more effective strategy in addressing the severity of hypermetabolism-hypercatabolism syndrome in pediatric sepsis. This technology reduced the duration and severity of systemic inflammatory response, as well as the manifestations and severity of multi-organ dysfunction on the background of sepsis in children of different age groups. Reduction in the activity of systemic inflammatory response against the background of combined pharmaconutritional support significantly improved the results of treatment of children with sepsis of various etiologies.

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