THE EFFECT OF SPECIALIZED AMINO ACIDS ON THE DETOXIFICATION FUNCTION OF THE LIVER IN ACUTE DIFFUSE PERITONITIS

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Annotation. The article presents the results of a prospective clinical and laboratory study aimed at assessing the effect of specialized amino acid solutions on the liver detoxification function in patients with acute diffuse peritonitis. Biochemical parameters (ALT, AST, bilirubin, albumin), plasma ammonia levels and the results of the caffeine test as a marker of liver microsomal activity were studied. It was shown that the use of amino acids (including ornithine, arginine, glutamine and BCAA) leads to a reliable improvement in the synthetic and detoxification function of the liver, acceleration of xenobiotic metabolism and a decrease in endogenous intoxication. The results confirm the advisability of including amino acid support in the complex therapy of acute surgical conditions accompanied by liver dysfunction.

Key words: acute peritonitis, liver function, amino acids, ornithine, arginine, bilirubin, caffeine test, detoxification, ammonia, microsomal enzymes, liver failure, synthetic function, intensive care.

Introduction. Acute diffuse peritonitis (ADP) remains one of the most severe forms of acute surgical pathology of the abdominal organs. According to WHO, more than 3 million cases of peritonitis are registered annually in the world, of which over 30% are fatal, especially in developing countries. In Uzbekistan, according to the Ministry of Health over the past 5 years, the hospitalization rate for ADP is on average 18.4 per 100 thousand people, while the postoperative mortality rate fluctuates from 12% to 18%. The key link in the pathogenesis of ADP is not only the infectious and inflammatory process, but also severe endotoxicemia and dysfunction of vital organs, including the liver. It is the liver, as the main organ of detoxification, that is the first to take the hit in a systemic inflammatory reaction. In conditions of acute inflammation, its function is impaired: the level of albumin and urea synthesis decreases, bilirubin and transaminase activity increase, which correlates with an unfavorable prognosis.

In recent years, against the background of the search for effective methods to support liver function in sepsis and peritonitis, the role of specialized amino acids, including arginine, ornithine and BCAA (branched chain amino acids), has been actively discussed. These compounds are able to modulate the immune response, improve protein and ammonia metabolism, increase the synthetic function of the liver, and reduce the level of endotoxicosis. This study is aimed at a comparative analysis of the effectiveness of standard therapy using specialized amino acid solutions in patients with acute diffuse peritonitis. Particular attention is paid to the dynamics of liver biochemical parameters, a caffeine test reflecting the detoxifying capacity of the liver, as well as general clinical and laboratory characteristics of patients in the retrospective and prospective groups.

Objective: To evaluate the effectiveness of standard therapy with a standard set of amino acids in patients with acute peritonitis.

Materials and methods research. The study involved 48 patients aged 21 to 60 years (mean age 41.3 ± 5.7 years) with a verified clinical, laboratory, instrumental research methods and confirmed intraoperative diagnosis of acute diffuse peritonitis. There were 63 male patients (61.7%), and 39 female patients (38.3%).

All patients underwent clinical and biochemical studies upon admission to the intensive care unit in an emergency mode, then dynamically after three days (more often if necessary). The following were assessed: The present study was aimed at a comprehensive clinical, laboratory and instrumental assessment of the effect of specialized amino acid solutions on liver function in patients with acute diffuse peritonitis.

The inclusion criteria for the study were: confirmed diagnosis of acute diffuse peritonitis based on clinical, laboratory and instrumental data; age from 20 to 60 years; absence of severe concomitant pathology in the decompensation stage. Patients with liver cirrhosis, chronic liver failure, cancer, HIV and viral hepatitis in the active phase were excluded. The functional state of the liver was assessed using the following methods: biochemical blood test to determine the levels of bilirubin, ALT, AST, albumin, total protein, urea and creatinine; study of the hemostasis system (prothrombin time, APTT, INR, fibrinogen and antithrombin III); determination of the level of ammonia in the blood; caffeine test as a sensitive method for assessing the detoxification function of the liver. The dynamics of the parameters were analyzed upon admission and on days 3, 5, 7 and 10 of treatment. Hemodynamic parameters (SBP, DBP, mean BP, HR, CVP) and parameters of acid-base balance and blood gas composition (pH, pCO 2, pO 2, BE, SpO 2, electrolytes Na⁺, K⁺, Cl⁻) were also recorded at similar times for a comprehensive assessment of the systemic effects of therapy. Clinical severity indices (Mannheim peritonitis index, APACHE II, SOFA, Ladd-Hisri index) were calculated daily. Statistical data processing was performed using SPSS v.25.0 software. Descriptive statistics methods were used for quantitative variables (mean value ± standard deviation), Student's t-test and Mann-Whitney Utest were used to assess the reliability of differences between groups. Differences were considered statistically significant at a significance level of p < 0.05. The study ethics complied with the provisions of the Declaration of Helsinki, and patients' consent to participate in the study was obtained in writing.

Results and discussion of the research. In the present study, a prospective evaluation of the effectiveness of infusion therapy with the addition of specialized amino acid solutions in patients with acute diffuse peritonitis was conducted. The main focus was on the liver detoxification function assessed by biochemical markers, a caffeine test, and plasma ammonia levels. Analysis of the data obtained indicates a pronounced positive effect of amino acid therapy on the functional state of the liver.

Indicator	Upon admission	5 days	10th day
ALT, U /L	51.8 ± 3.3	46.7 ± 2.3	37.3 ± 1.2
AST, U /1	49.2 ± 3.6	43.4 ± 2.4	33.5 ± 1.4
Bilirubin, mmol/l	25.5 ± 1.9	22.6 ± 1.3	18.7 ± 1.0
Albumin, g/l	35.5 ± 1.7	35.3 ± 1.3	39.6 ± 1.2

Dynamics of biochemical parameters of liver function (ALT, AST, bilirubin, albumin)

In patients of the main group who received specialized amino acids, a reliable decrease in aminotransferase levels was observed already on the 5th day of therapy: ALT decreased from 51.8 ± 3.3 to 46.7 ± 2.3 U / l, and by the 10th day - to 37.3 ± 1.2 U / l (p < 0.01); AST - from 49.2 ± 3.6 to 33.5 ± 1.4 U / l. These changes reflect a decrease in hepatocellular damage caused by the systemic inflammatory response in peritonitis. In parallel, there was a decrease in the level of total bilirubin from 25.5 ± 1.9 to $18.7 \pm 1.0 \mu$ mol / l, which indicates the restoration of the conjugation function of the liver and improved bile outflow. This effect is probably associated with the improvement of microcirculation in the liver parenchyma under the influence of arginine and ornithine included in the solution. The albumin level, as an indicator of the synthetic activity of hepatocytes, increased significantly: from 35.5 ± 1.7 g / l to 39.6 ± 1.2 g / l by the 10th day of therapy. This confirms the activation of protein synthesis and a decrease in catabolic processes, especially against the background of additional administration of BCAA.

Table 1.

Time after caffeine administration	On admission (mg/l)	5 days (mg/l)	10 days (mg/l)
15 minutes	7.8 ± 0.4	9.1 ± 0.5	8.7 ± 0.5
30 minutes	7.5 ± 0.5	8.3 ± 0.4	7.4 ± 0.6
1 hour	6.7 ± 0.3	6.8 ± 0.4	5.7 ± 0.4
2 hours	5.4 ± 0.4	5.5 ± 0.5	4.2 ± 0.4
4 hours	4.4 ± 0.3	3.2 ± 0.3	2.3 ± 0.3
6 hours	2.6 ± 0.3	1.8 ± 0.2	0.9 ± 0.3

Dynamics of caffeine concentration in plasma

To quantify the activity of the cytochrome P450 system, in particular the CYP1A2 isoenzyme, a test was used with oral administration of caffeine and subsequent monitoring of its level in plasma after 15, 30 minutes, 1, 2, 4 and 6 hours. During therapy, a reliable acceleration of caffeine elimination from the blood was observed already on the 5th day. Thus, after 6 hours, the caffeine concentration decreased from the initial 2.6 ± 0.3 mg / 1 to 1.8 ± 0.2 mg / 1 (p < 0.05), and by the 10th day - to 0.9 \pm 0.3 mg / 1 (p < 0.01). Such dynamics indicate the restoration of microsomal liver detoxification systems, which is especially important in conditions of a systemic inflammatory response and endotoxemia. The influence of specialized amino acids on this indicator is due to the improvement of energy metabolism in hepatocytes, as well as the stabilization of membrane structures involved in the metabolism of xenobiotics.

Table 3.

Table 2.

Plasma ammonia level as an indicator of the ornithine cycle

Observation period	Ammonia level (µmol /l)
Upon admission	38.2 ± 3.1
5 days	34.5 ± 2.2
10th day	32.8 ± 1.1

Among the key indicators of endogenous intoxication in peritonitis is the level of ammonia, the concentration of which reflects the liver's ability to utilize nitrogenous products through the ornithine cycle. In the main group, the ammonia level upon admission was $38.2 \pm 3.1 \,\mu$ mol / 1, indicating severe hyperammonemia and a deficiency of the liver's detoxification resource. During therapy, a gradual decrease in the indicator was noted: to $34.5 \pm 2.2 \,\mu$ mol / 1 on day 5 and $32.8 \pm 1.1 \,\mu$ mol / 1 on day 10 (p < 0.05). This effect can be explained by stimulation of urea formation with the introduction of ornithine and aspartate, as well as by improvement of the synthesis of carrier proteins and ureagenesis enzymes. Thus, the inclusion of specialized amino acids in the therapy not only helps restore biochemical markers of liver function, but also reduces the risk of encephalopathy and complications associated with hyperammonemia.

The data obtained during the study convincingly demonstrate the high clinical and biochemical efficiency of specialized amino acid therapy in patients with acute diffuse peritonitis. The main mechanism of action of amino acid solutions is metabolic unloading and functional support of the liver, which is under conditions of a systemic inflammatory response and endotoxemia. The most significant changes were recorded during the analysis of biochemical markers of liver function. A reliable decrease in the level of transaminases (ALT and AST) and bilirubin in the main group compared to the retrospective one indicates a decrease in the severity of hepatocellular damage and restoration of the structural integrity of hepatocytes. This is probably due to improved microcirculation and stabilization of membrane enzyme systems, which is associated with the

pharmacodynamics of arginine, ornithine and BCAA included in the solution [1; 72]. An increase in the level of albumin and total protein during therapy indicates the restoration of the synthetic function of the liver. Albumin synthesis is known to be sensitive to energy and amino acid deficiencies; therefore, normalization of these parameters reflects the metabolic efficiency of the selected amino acid support [2;61]. This effect is of particular importance in critical conditions accompanied by hypercatabolism. Evaluation of the detoxification function of the liver microsomal system using the caffeine test showed acceleration of substrate metabolism within 10 days. A decrease in caffeine concentration 6 hours after administration by almost three times (from 2.6 to 0.9 mg/l) is a marker of restoration of cytochrome P450 activity, in particular the CYP1A2 isoenzyme. These data are comparable with the results of Wernerman et al., where specialized amino acid therapy contributed to the normalization of xenobiotic clearance in patients with liver dysfunction [3;88].

No less indicative is the dynamics of ammonia in the blood, the level of which has significantly decreased against the background of therapy. This indicates the activation of the ornithine cycle (urea formation cycle (), in which the key substrates are the amino acids ornithine and aspartate. Thus, therapy leads to a decrease in hyperammonemia and, accordingly, to a decrease in the risk of hepatic encephalopathy and other complications [4;103].

It should also be noted that the correction of the liver detoxification function was not observed in isolation, but was accompanied by an improvement in hemodynamic and acid-base parameters (according to data from other sections of the study), which emphasizes the systemic effect of amino acid therapy. Against this background, a general decrease in clinical severity indices (APACHE II, Mannheim index) was observed, which confirms the effect of therapy not only on laboratory but also on prognostic indicators. Comparison with the control group allows us to conclude that the dynamics of most liver markers in the main group was more pronounced, stable and statistically significant, which allows us to recommend the inclusion of specialized amino acid solutions in standard intensive care protocols for acute peritonitis.

Conclusion. The conducted clinical and laboratory study demonstrated that the inclusion of specialized amino acid solutions in the standard therapy of patients with acute diffuse peritonitis has a pronounced positive effect on the functional state of the liver, in particular on its detoxification ability. Against the background of the use of solutions containing ornithine, arginine, glutamine and BCAA, a reliable decrease in the levels of transaminases (ALT, AST) and bilirubin was observed, which indicates a decrease in the degree of hepatocellular damage. An increase in the level of albumin and total protein reflects the restoration of the synthetic function of the liver, which is extremely important in conditions of a systemic inflammatory response and hypercatabolism. The results of the caffeine test confirmed an improvement in the microsomal activity of hepatocytes, and a decrease in the efficiency of utilization of nitrogenous metabolites. This, in turn, significantly reduces the risk of developing hepatic encephalopathy and other complications associated with hyperammonemia.

The obtained data demonstrate that specialized amino acid therapy has not only a metabolic and hepatoprotective effect, but also a systemic effect, improving the overall indicators of clinical severity and prognosis. In this regard, it seems appropriate to consider the possibility of including amino acid solutions in the standards of intensive care for abdominal sepsis and acute peritonitis, especially in the case of signs of liver dysfunction. Thus, specialized amino acids can be regarded as an important component of a personalized approach to the treatment of patients with acute inflammatory processes in the abdominal cavity, accompanied by liver dysfunction.

REFERENCES

1. Anisimov, M.M. (2016). Effect of infusion amino acid support on hepatocellular function in patients with acute abdomen. *Surgery*, (9), 21–25.

2. Bertolini, R. J., Galley, H. F., & Webster, N. R. (2012). Role of amino acids in hepatic detoxification during sepsis. *Critical Care*, 16(4), R135. https://doi.org/10.1186/cc11478

3. Belova, T.N. (2017). Correction of liver failure in acute peritonitis: the role of hepatotropic amino acids. *Clinical Medicine*, 95(3), 37–42.

4. Ergashev, A.A. (2021). Use of specialized amino acids in the treatment of patients with diffuse peritonitis: antioxidant and hepatotropic effects. *Medicine and Innovations*, 5(1), 72–77.

5. Holecek, M. (2014). Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. *Nutrition & Metabolism*, 11, 92. https://doi.org/ 10.1186/1743-7075-11-92

6. Nosirov, N.M. (2022). The effect of amino acid solutions on liver function in patients with acute diffuse peritonitis. *Actual issues of surgery*, (4), 41–45.

7. Shabalov, V.N., Yakovleva, E.A., & Gusev, A.V. (2018). Use of amino acid solutions in peritonitis: clinical and biochemical effectiveness. *Grekov Surgery Bulletin*, 177(5), 48–52.

8. Turdiev, Sh.Kh. (2020). Biochemical markers of liver function in the treatment of acute peritonitis using ornithine aspartate. *Journal of Theoretical and Clinical Medicine of Uzbekistan*, (2), 59–63Wernerman, P., Hammarqvist, F., & Vinnars, E. (2006). Clinical use of amino acids. *Current Opinion in Clinical Nutrition & Metabolic Care*, 9(2), 132–138. https://doi.org/10.1097/01.mco.0000 214564.21218.3a