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Hepatoprotection in the intensive care unit patients with purulent-septic infection.

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Clinical-laboratory and instrumental analysis of the course of purulent-septic pathology associated with "diabetic foot" syndrome and acute diffuse peritonitis was performed in 38 patients randomized according to the type of intensive therapy (with and without hepatoprotection). Liver involvement in the process and its disfunction was shown in the study. Adding "Jetepar" as a liver protecting agent to intensive therapy measures, with all other conditions being equal, allowed to achieve earlier and more significant improvements in impaired protein-synthesizing and detoxicating functions of liver as well as improvements of plasma and platelet hemostatic parameters.

Keywords: liver, hepatic insufficiency, endotoxemia, hepatoprotection, hemostasis.

A steady increase in the number of patients with acute and chronic liver diseases has been shown recently. Annually, more than 2 million people worldwide die due to liver failure, characterized by gross inconsistencies between the needs of the body and the functionality of the liver [5]. This trend is applicable to Uzbekistan, where hepatopathy is a regional problem.

Apart from the main and the most common causes of liver failure (LF) - viruses, alcohol, hepatotropic poisons, - significant liver disfunction is a frequent phenomenon in the practice of emergency surgery [2].

Patients of intensive care units (ICU) in critical condition often suffer from development of multiple organ failure syndrome, significantly worsening the prognosis. One of the most frequently impaired organs is liver, affected in critically ill patients by the vast majority of pathological factors.

The etiopathogenesis of liver damage in critically ill patients is multicomponent [3]. The cause of liver damage primarily can be the conditions, which led to admission of patients in the ICU, especially with severe purulent - septic infection. In addition, usage of a large number of medicines (usually, polypharmacy) in patients of ICU causes toxic medicinal liver damage (MLD). According to the literature, medicinal liver damage accounts for 10% of all adverse drug reactions [7,8,11]. However, the real prevalence of MLD appears to be higher [3,10]. Up to 40% of all cases of diagnosed hepatitis, and more than 50% of cases of hepatitis in patients aged 40 or older are drug-induced [12,5]. Many researchers confirmed presence of liver function disorders, as well as its diffuse or focal lesions in all critically ill patients [9]. In 11% of ICU patients, acute liver failure develops within the first 48 hours after admission to the department, and subsequently it progresses, increasing the in-hospital mortality by 2 times [3]. Therefore, strictly differentiated intensive therapy procedures based on pathogenetic features of development of liver and liver-and-renal failure, early diagnosis of liver involvement into the pathological process, and assistive correction of its impaired functions, can reduce progression of the disease and risk of development of severe forms of liver failure [6].

The aim of study: prevention and early detection of functional liver disorders in patients with purulent-septic infection and its timely correction.

Materials and methods:

During 2017, 38 patients with severe purulent septic infection associated with diabetic foot syndrome (20), acute peritonitis (18) of appendicular origin (8 patients) associated with acute destructive pancreatitis (7 patients) and blunt abdominal trauma with rupture of small intestine (3 patients) were admitted for treatment in the ICU of Tashkent Medical Academy. All patients had generalization of the infection with sepsis development (30 patients) and septic syndrome (8 patients). The age of patients varied between 21 and 47 years, being at average 36.7±4.1 years. By gender, there were 18 female and 20 male patients.

All patients underwent surgery with elimination of the main infection source or its complete drainage (in cases of destructive pancreatitis).

All patients had disseminated intravascular clotting (DIC) syndrome without its significant manifestation. All patients received intensive therapy in pre- and post-surgery period: correction of vital organs function, antibacterial therapy, infusion-transfusion therapy, detoxification, DIC control, adequate analgesia, diuretics, d-bridement of surgical wound and symptomatic therapy.

The patients who were included into the study were divided into 2 groups, consisting of 19 patients each: (I -control group - archive data and II - study group) by the only factor: patents of study group were prescribed Jetepar manufactured by Popular Chemical Works (Pvt.) Ltd, Pakistan (under license: Rotta Reasearch Laboratorium, Milan, Italy) for liver protection in addition to the above mentioned therapy. This drug was administered intravenously as a drip. The daily dosage - 30 ml per day to maintain the functional state of hepatocytes exposed to the expressed effect of numerous toxic factors (purulent-septic infection, intoxication, surgical interventions, medicines). The number of pharmacological agents prescribed to every patient was 14-23, on average 18±2 (antibiotics, analgesics, NSAIDs, parenteral nutrition, metabolics, hormones, antifungal agents, vasopressors,

infusion media, etc.). 18 patients with peritonitis received complete parenteral nutrition. The rest patients received mixed artificial nutrition accounted as protein - 1.5-2 g/kg, carbohydrates 3 g/kg, and fats 1-2 g/kg weight. Protein calories were not included into the overall calories counting. In both groups, in order to normalize protein metabolism, specialized amino acid mixture Acumin-Hepa containing branched-chain amino acids (42%) and significantly reduced in aromatic amino acids was infused intravenously.

According to prescribing information, Jetepar has liver-protective and antitoxic effect due to its ingredients: betaine glucuronate (glucomethamine) and diethanolamine glucuronate (glucodiamine).

The criterion for non-inclusion of patients into this study were lethal cases and severe complications (bleeding, pneumonia, pulmonary embolism, non-curable peritonitis, etc.).

Groups of patients were randomized in all respects, which allowed us to compare the obtained data.

Study methods. During the intensive care therapy all patients underwent clinical and laboratory tests of blood and urine, biochemical tests (bilirubin, nitrogen waste products, total protein, protein fractions (electrophoresis), fibrinogen (through Rutberg's method), AsAT, AlAT (Reitman-Frenkel method), bilirubin (according to Iendrashek) and its fractions, blood electrolytes, medium-molecular peptides blood levels (in optical units).

When necessary, ultrasound, CT of abdominal organs, ECG control, duplex examination of deep veins of the lower limbs and pelvis were performed for patients to exclude thrombosis.

Stages of the study: on the day of admission and on daily basis while patients were in the ICU. All the data obtained were subjected to statistical analysis using standard methods of variational statistics.

Results and discussion.

Patients of both groups were admitted in a severe condition associated with the main pathology, purulent-septic intoxication, hypovolemia, established organs and systemic disorders caused by generalization of the process.

Almost all patients had liver enlargement. Patients complained of weakness, dyspeptic disorders (21 patients), pruritus (13 patients), jaundice (4 patients), soreness and heaviness sensation in the right hypochondrium (29 patients).

Clinical-and-laboratory studies found anemia, hypoproteinemia with decrease in albumin levels in blood, and moderate thrombocytopenia. The indices of nitrogen waste products in blood, serum transaminases and bilirubin were within physiological values, but at the upper limit of the normal range.

Table 1.

Clinical and laboratory data of patients of both groups upon admission (n = 38).

№	Tests	Control group	Study group
1	Hemoglobin, g/l	94.7±2.4	91.3±1.9
2	Erythrocytes, 10^{12}/l	2.9±0.2	2.8±0.1
3	Leucocytes, 10^{9}/l	11.4±0.9	12.0±0.5
4	Lymphocytes, %	13.7±1.1	14.1±0.9
5	Total protein, g/l	56.3±3.4	54.4±2.7
6	Albumin, %	41.1±1.0	39.8±1.3
7	Globulins, %	59.9±2.4	60.2±1.4
8	Fibrinogen, g/l	3.5±0.3	3.6±0.4
9	Serum creatinin, μmol/l	145.9±3.7	151.7±4.0
10	Urea, mmol/l	13.4±0.9	13.8±1.2
11	AsAT, μmol/(h*ml)	0.51±0.04	0.49±0.02
12	AlAT, μmol/(h*ml)	0.78±0.05	0.76±0.06

13	Medium molecules	0.78±0.04	0.80±0.04
14	Glucose, mmol/l	11.2±1.1	10.7±0.9
15	Potassium, mmol/l	5.4±0.3	5.2±0.4
16	Sodium, mmol/l	146.0±1.1	142.9±1.6
17	Total bilirubin, μmol/l	14.7±2.1	16.9±1.7
18	Direct reacting bilirubin, μmol/l	3.1±0.4	4.4±0.3
19	Indirect reacting bilirubin, μmol/l	11.6±1.7	12.5±1.4

The data obtained shows that in the both groups of patients, at the time of admission, besides anemia, hypoproteinemia and decrease of A/G coefficient (0.68, 0.66, respectively), an increase in nitrogen waste products levels in blood, indicating kidneys dysfunction, and lymphopenia, which is indirectly associated with decrease of the immune response of patients to purulent septic infection were noted. The increased activity of transaminases in blood of patients of both groups reveals necrobiotic processes in the body, primarily in kidneys and liver, as indicated by hypoalbuminemia and high levels of medium-molecular peptides in blood.

Increased blood glucose level (averaged data by groups) was shown entirely due to that in patients with diabetes mellitus (DM). In patients without diabetes, the average values of blood glucose at admission were within the range of 3-4 mmol/l.

In order to verify the DIC syndrome, to determine its stage and to assess the degree of hepatic dysfunction associated with hemostasis, all patients' coagulograms were analyzed at admission. The results obtained are presented in the table below.

Table 2.

Indicators of hemostasis upon admission in patients of both groups.

№	Test	Groups			
		Control (n=19)		Study (n=19)	
1	Blood clotting time by Sukharev	beginning	5.3±0.2	beginning	5.7±0.3

	(minutes)	end	6.7±0.4	end	6.9±0.3
2	ISR (International Standardized Ratio)	1.52±0.2		1.56±0.2	
3	Plasma recalcification time (sec)	167.9±4.4		170.1±4.2	
4	Plasma tolerance to heparin (minutes)	17.7±1.8		18.4±0.9	
5	Protrombin index, %	67.6±2.4		65.9±3.0	
6	Thrombocytes, $10^9/mm^3$	182.7±3.9		186.0±2.7	
7	Thrombotest, degree	3.7±0.3		3.6±0.2	
8	Fibrinogen (colorimetric method), g/l	3.2±0.4		3.4±0.4	
9	Plasma fibrinolytic activity (minutes)	407.6±10.1		413.3±7.6	
10	Fibrin degradation products (FDP)	+		+	
11	Activated partial thromboplastin time (APTT), sec	61.9±4.3		60.7±3.9	

The given data state the presence of DIC syndrome, as evidenced by the positive FPD reaction. Changes in plasma and platelet hemostatic parameters with relatively normal values of fibrinogen indicate the transition of stage II to stage III – the stage of hypocoagulation and directly or indirectly indicate the involvement of liver into hemostasis disorders. Our data on primary liver damage in patients with purulent-septic infection after surgical interventions (without any previous history of liver function disorders) are in full agreement with the definition of the causes of hepatic failure stated at the consensus of the Asian Pacific Association for the Study of the Liver (APASL, 2014) and Ermolova T.V. et al. (2009). The factors of development of acute liver failure in ICU patients are the following: traumatic surgery, infection, endotoxemia, and medicines. These factors were encountered in the development of hepato-, nephro-and cerebro-toxic effect in patients examined in our study.

Table 3 presents data on the dynamics of changes in clinical and laboratory parameters in the control group and the study group, where in addition to the standard treatment, Jetepar was prescribed to patients for liver rotction.

Table 3.

Dynamics of clinical and laboratory indicators in the process of intensive therapy by groups

№	Test	Time after surgery (days)		
		I	III	V
1	Hemoglobin, g/l	87.2±0.2	93.1±1.3*Δ	96.6±1.4*Δ
		82.6±0.3	98.4±1.5*	99.8±0.7*
2	Leucocytes, 10^9/l	13.7±0.6	11.8±0.7	10.1 ±0.4*Δ
		12.4 ± 0,4	12.6 ± 0,8	10.8 ± 0,3*Δ
3	Lymphocytes, %	11.6±0.3	13.3±0.4*Δ	18.7±1.0*Δ
		9.4±0.4	17.9±0.7*	24.0±2.1*
4	Total protein, g/l	52.9±2.7	59.7±1.4*	62.0±0.7*Δ
		53.7±3.0	63.4±2.0*	65.9±1.9*
5	Albumin, %	39.8±2.7	42.1±1.4Δ	44.3±1.1Δ
		40.4±3.1	49.9±1.6*	57.7±2.3*
6	Creatinine, μmol/l	160.4±4.1	119.4±3.7*Δ	99.8±1.4*Δ
		157.9±3.3	103.6±2.9*	90.1±1.2*
7	Urea, mmol/l	12.7±1.2	10.6±0.9	9.8±0.7
		10.9±0.8	9.4±0.4	8.4±0.4
8	AsAT, μmol/(h*ml)	0.54±0.05	0.41±0.02*Δ	0.35±0.02*
		0.56±0.03	0.33±0.02*	0.30±0.01*
9	AlAT, μmol/(h*ml)	0.63±0.05	0.60±0.02	0.52±0.02*
		0.66±0.04	0.55±0.03*	0.50±0.03*
10	Medium molecules, optic units	0.80±0.03	0.62±0.02*Δ	0.49±0.03*Δ
		0.79±0.04	0.54±0.03*	0.41±0.02
11	Potassium, mmol/l	5.0±0.4	4.6±0.3	4.3±0.2*
		5.2±0.3	4.8±0.2	4.1±0.3
12	Sodium, mmol/l	149.1±1.3	146.9±1.7	147.0±1.6
		145.3±1.1	144.4±1.0	142.3±1.4
13	Bilirubin, μmol/l	16.9±2.3	13.1±1.7	11.1±0.7*
		21.7±2.7	12.8±0.9*	10.6±0.7*
14	Glucose, mmol/l	12.3±0.9	9.5±0.9*	8.2±0.6*
		10.7±0.7	8.6±0.4*	7.8±0.3*

Note: data presented as data of patients of the control group (in numerator),

and data of patients of the study group (in denominator)

Δ – significant difference between groups of patients on study day ($p < 0.05$)

* - significant difference comparing to the first day of the study ($p < 0.05$).

The data presented show positive effect of intensive therapy on clinical and biochemical blood parameters in both groups of patients, which corresponded to clinical manifestations.

A detailed analysis of the results shows more significant improvements in patients of the study group who demonstrated positive changes in almost all blood tests indicated in the table already by the third and especially by the fifth day. Increase in total protein level in blood on the fifth day after surgery, mainly due to albumins, decrease in predictors of endotoxemia – medium-molecular peptides levels, decrease in transaminase activity, normalization of azotemia level by the fifth day show improvement of function of liver and kidneys.

Regardless of the causes of liver failure previous guidelines recommended protein restriction. We, in our actions, adhered to recommendation of ESPEN Guidelines on Parenteral Nutrition: Hepatology [15]. To maintain the nitrogen balance, we used a special combination of amino acids in dose of 1.5-2.0 g/kg/day. Also, the review by Plotnikova E.Yu. (2013) shows that in patients with acute liver failure, excessive protein restriction leads to elevation of blood ammonia level as a result of activation of muscle catabolism [16].

However, comparing the treatment results data in the two groups it can be noted that restoration of the blood parameters in the study group occurs somewhat earlier (already by the third day) and are more significant, which, other things being equal, evidences a positive effect of liver protecting action of "Jetepar". So, if by the fifth day, the total protein level in blood of patients in Group I increased by 17.2%, in the IInd group this increase was higher - by 22.7%, and albumin level increased by 11.3% and 42.8%, respectively, which clearly demonstrates restoration of protein-synthesizing function of liver with the background of significant decrease in necrobiotic processes in liver, as indicated by AlAT and AsAT levels decrease by 17.5, 24.3% and 35.2, 46.5%, respectively, by the fifth day. Decrease in the level of medium molecules in both groups by the fifth day

was 38.8% and 48.2%, respectively, which may also evidence improvement in detoxificating function of liver and in the functional state of kidneys.

We also noted positive dynamics in hemostatic parameters.

Table 4

Dynamics of hemostasis tests during intensive therapy by groups.

№	Test	Time after surgery (days)			
		I		III	V
1	Blood clotting time by Sukharev (minutes)	Beginning	5.47±0.4	5.51±0.4	6.01±0.3
			5.35±0.4	5.40±0.3	5.58±0.4
		End	6.30±0.3	6.32±0.4	6.46±0.4
			5.55±0.4	6.01±0.3	6.08±0.4
2	Plasma recalcification time (sec)	152.4±3.9		146.9±2.1	137.8±3.1
		156.1±4.0		132.2±3.0	112.0±2.0
3	Plasma tolerance to heparin (minutes)	18.0±0.3		17.5±0.4	17.0±0.3
		17.9±0.2		15.6±0.3	14.4±0.2
4	Protrombin index (%)	59.2±1.9		62.4±1.5	70.8±1.9
		58.4±2.1		65.2±1.3	71.2±2.1
5	Thrombocytes 10^9/мм^3	167.4±4.1		172.0±4.2	188.1±4.0
		170.1±3.6		186.6±3.9	204.6±3.9
6	Thrombotest (degree)	3.6±0.2		3.8±0.2	4.0±0.3
		3.4±0.1		4.1±0.3	6.1±0.3
7	Fibrinogen, g/l	346.6±2.7		335.5±4.0	296.5±3.6
		349.7±4.3		313.1±3.7	287.1±2.9
8	Plasma fibrinolytic activity (minutes)	377.9±8.4		341.0±6.2	311.2±4.7
		390.1±9.2		297.1±5.1	224.8±3.9
9	APTT (sec)	57.9±2.7		56.6±3.0	56.2±3.1
		60.1±2.5		50.4±2.7	47.0±2.2
10	ISR	1.5±0.3		1.4±0.2	1.1±0.1
		1.4±0.2		1.1±0.1	0.9±0.2

Note: data presented as data of patients of the control group (in numerator), and data of patients of the study group (in denominator)

The data presented in the table indicate that on the first day following surgery, plasma and platelet factors were shifted toward hypocoagulation, indirectly indicating a deficiency of hepatic factors of hemostasis.

During intensive care therapy, hemostasis parameters started improving on the third day, but the positive changes were more significant in the study group, which

also indicates efficacy of Jetepar used in this group for liver protection. The more significant and earlier medium-molecular peptides levels decrease in patients of the study group may prove a detoxicating effect of this drug.

All types of pathogenic mechanisms of liver damage are characterized by damage of hepatocytes accompanied by inflammation, cytolysis and development of fibrosis. The basic pathogenic therapy in these cases is use of medicines affecting the structure and function of hepatocytes. These are the medicines called liver protecting agents/hepatoprotectors. Jetepar was used as a part of complex therapy in patients with purulent-septic infection and contributed to the increase in resistance of hepatocytes (resulted in decrease of transaminases activity) to damaging factors, restored their detoxifying function (decrease in the level of medium-molecular peptides, improved urea synthesis function), promoted restoration of protein-synthesizing function of hepatocytes and their participation in the hemostasis system. The data obtained by us coincide with those cited in the literature on the positive effect of hepatoprotectors in prevention of liver impairment in critically ill patients [17,18,19].

The data presented confirm the hepatoprotective and detoxicating role of "Jetepar" (Popular Chemical Works (Pvt.) Ltd, Pakistan) in case of severe purulent septic infection; this medicine may be recommended for use as a part of complex therapy of such critical conditions with the purpose of providing supporting therapy and prevention of liver complications development.

Conclusions:

1. Functional liver disorders due to the numerous pathological factors affecting hepatocytes, such as infection, intoxication, surgical intervention, and numerous medications, play the leading role in organ and systemic dysfunction in patients of ICU with purulent-septic infection.

2. The most common liver disorders are: disorders of detoxification, protein-synthesizing function and hemostasis.

3. Prevention and early correction of conditions which may develop as a result of hepatocytes damage require a complex influence on pathogenic mechanisms of functional liver disorders development.

4. Using drugs reducing the toxic load and affecting the mechanisms of hepatoprotection is an effective way to correct liver dysfunction.

5. “Jetepar” has liver protecting and detoxicating effect, affecting hepatocytes, reducing dystrophic changes in liver cells (as evidenced by normalization of transaminases activity and decrease in medium-molecular peptides level in blood) and increasing their resistance to damaging factors.

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