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ASSESSMENT OF DISORDERS OF THE COAGULATION LINK OF HEMOSTASIS IN PATIENTS WITH CHRONIC HEPATITIS AND LIVER CIRRHOSIS OF VIRAL ETIOLOGY.

KurbonovaZ.Ch.,
Babadjanova Sh.A.,
Nuriddinova N.F.
Tashkent Medical Academy

ABSTRACT

The objective of the research is to carry out comparative clinical and laboratory characteristics of coagulopathy in patients with liver cirrhosis of viral etiology.

Materials and methods: clinical studies were carried out in the hepatobiliary department of the Tashkent medical academy. The study included 80 patients with liver cirrhosis of the viral etiology, in the stage of decompensation of class B according to Child-Pugh, 41 patients with chronic hepatitis of the viral etiology,and 20 patients with liver cirrhosis of non-viral etiology.

Results: the decrease of blood coagulation system activity is more pronounced in the group with liver cirrhosisviral etiology, in contrast to non-viral liver cirrhosis.

Keywords: hemostasis, coagulopathy,hypocoagulation, liver cirrhosis, chronic hepatitis, hemorrhage syndrome.

INTRODICTION

Over the past decades, the incidence of liver cirrhosis has remained consistently high and amounts to 30% of the total number of patients with chronic diffuse liver diseases treated in specialized hospitals. In 50-85% of patients, cirrhosis of the liver is complicated by portal hypertension, the manifestation of which is varicose veins (VRV) of the esophagus and cardia of the stomach. Bleeding from VRV occurs in every fourth patient, reaching 50-70% mortality already in the first episode. [5].

The proportion of viral etiology of liver cirrhosis (in the outcome of chronic hepatitis B, C, B+D) ranges from 10 to 23.5% of all cirrhosis [4, 15]. In recent years, the number of cirrhosis in the outcome of viral hepatitis C has increased to 30.3% [3, 12].

The liver plays a key role in hemostasis; therefore, diffuse lesions of its parenchyma lead to complex disorders of blood coagulation [17]. Currently, it is believed that changes in hemostasis in liver cirrhosis affect the pro- and anticoagulant systems, while maintaining a balance between them, but due to the reduced reserve of each of these systems, it is easily shifted towards hypo- or hypercoagulation [16, 19].

Over the past two decades, autoimmune diseases of the liver have received increasing attention [9]. Many pathogenetic aspects of pathogenetic disorders in chronic liver diseases remain unexplored [18, 14]. One of the most common causes of chronic hepatitis and liver cirrhosis is infection with hepatitis B and C [6, 8, 10].

At the same time, more than 180 hepatotoxic drugs have been identified, of which 6 groups seriously injure the liver. At the same time, 50% of drugs are hepatotoxic, especially in women this effect is more pronounced. Medicines cause hepatocellular damage, even liver necrosis, which is clinically manifested mainly by jaundice, fever, and increased liver enzymes [13].

Autoimmune hepatitis remains hepatitis of unknown etiology, because many medical institutions do not have special examination methods, and one third of patients are referred after the development of liver cirrhosis. Autoimmune hepatitis can be suspected in any patient with acute or chronic liver disease. 80% of patients have a recurrence of the disease after canceling the treatment [20]. Timely diagnosis of chronic hepatitis and liver cirrhosis and appropriate will reduce the risk of many complications [1, 2, 7].

In liver cirrhosis, changes in the hemostasis system are complex and multidirectional. Complex and ambiguous changes in the hemostasis system in patients with impaired liver function can lead to various complications. Bleeding is the most common clinical manifestation, both due to thrombocytopenia and thrombocytopathy, and due to impaired synthesis of coagulation factors, as well as activation of fibrinolysis [11].

Developments on a comprehensive assessment of hemostatic homeostasis disorders in chronic liver pathology are in the process of finding a solution to this problem. Many pathogenetic aspects of hemorrhagic syndrome and the role of hemostatic changes in it in chronic liver diseases remain unexplored.

Timely diagnosis of hemostasis disorders in patients with liver cirrhosis of viral etiology and appropriate hemostatic therapy will reduce the risk of hemorrhagic complications. For this reason, we undertook this study.

PURPOSE OF THE STUDY

To conduct a comparative clinical and laboratory characterization of coagulopathy in patients with chronic hepatitis and liver cirrhosis of viral etiology.

MATERIAL AND RESEARCH METHODS

Clinical studies were carried out in the hepatobiliary department of the 1st clinic of the Tashkent Medical Academy. The study included 80 patients with liver cirrhosis of viral etiology, in the stage of Child-Pugh class B decompensation, 41 patients with chronic viral hepatitis of moderate activity, and 20 patients with liver cirrhosis of non-viral etiology. Group I consisted of 30 patients with cirrhosis with a positive hepatitis B virus, group II - 20 patients with cirrhosis with positive hepatitis B and D viruses, group III - 30 patients with cirrhosis with a positive result of hepatitis C virus, group IV of patients consisted of 20 patients with liver cirrhosis of non-viral etiology. V and VI groups included 21 patients with viral hepatitis B and 20 patients with viral hepatitis C, respectively.

Of these, 80 (56.74%) men and 61 (43.26%) women. The age of the patients ranged from 21 to 69 years, the average age of the examined was 49.2 ± 13.3 years. All patients had a long-term chronic liver disease, the duration of cirrhosis averaged 4.15±1.74 years. Among patients, persons of reproductive age accounted for 43.97%.

The control group consisted of 20 patients who did not suffer from diseases of the liver and biliary tract, with negative results for markers of hepatitis B and C.

Hematological, hemostasiological research methods, as well as methods of variation statistics were used. Hematological studies were carried out on a Mindray 3000 hematological analyzer (China), microscopic studies of platelets were carried out on a Micromed light microscope (Russia), acoagulogram was studied on a Mindraycoagulometer using a Human reagent kit.

RESULTS OF THE STUDY

To study the plasma link of hemostasis, plasma coagulation factors of a protein nature and produced in the liver were studied. The protein-forming function of the liver in the patients examined by us was reduced.

Coagulation hemostasis is a cascade of reactions involving plasma coagulation factors. The process of thrombus formation is conditionally divided into 3 phases.

To assess the first phase of blood coagulation, the Moravitz clotting time and APTT were studied (Table 1).

APTT is a test that detects exclusively plasma defects in the internal system of factor X activation in the first phase of blood coagulation. Prolongation of APTT reflects a deficiency of plasma factors XII, XI, IX, VIII and is observed with their significant decrease (below 10-25%) and indicates the predominance of hypocoagulation, which was reliably shown in groups I and II. In groups III and IV, APTT was slightly increased, which had no clinical significance, and the parameters of groups V and VI were identical to those in the control group.

A pronounced prolongation of blood clotting time is observed with a deep deficiency of blood clotting factors. The clotting time (CT) was also significantly prolonged in groups I and II. In groups III and IV, CT was slightly lengthened, and CT indicators of groups V and VI corresponded to the data of the control group.

Table 1. Assessment of the first phase of blood coagulation in liver cirrhosis and chronic hepatitis of viral etiology

Groups	CT start, sec	CT end, sec	APTT, sec
Control groupn=20	125 ±12.5*	248 ± 13.2*	29.1 ± 2.24*
Group I, n=30	352 ± 23.2*	482 ± 32.5*	39.4 ±3.01*
Group II, n=30	372 ± 26.5*	488 ± 29.8*	41.0 ± 6.80*
Group III, n=20	212 ± 13.4*	306 ± 19.7*	36.57 ± 2.55*
Group IV, n=20	139± 9.4*	248± 11.9*	36.5 ± 1.25*
Group V, n=21	119±8.8*	230±7.8*	28.8 ± 2.75 *
Group VI, n=20	116±6.4*	224 ± 6.6*	27.8 ± 1.78*

Note: *- $p < 0.05$ significantly in relation to the control group.

As can be seen from the table, pronounced violations of the first phase of plasma hemostasis were present in patients with liver cirrhosis B and V + D of viral etiology, while in patients with liver cirrhosis C of viral etiology and non-viral etiology, these indicators were slightly shifted towards hypocoagulation, and in chronic viral hepatitis B and C, these indicators were within the normal range and did not significantly differ from the control group.

To study the second phase of the plasma link of hemostasis, prothrombin time, prothrombin index and INR were determined.

Prothrombin time characterizes the first and second phases of plasma hemostasis and reflects the activity of the prothrombin complex - factors VII, V, X and prothrombin - factor II. An increase in prothrombin time indicates a tendency to hypocoagulation. Studies have shown a significant shift in the hemostasis system towards hypocoagulation in patients of groups I and II, while patients in groups III and IV tended to hypocoagulation, and the indicators of patients in groups V and VI were close to the control group.

The prothrombin index, calculated from the indicators of prothrombin time, reflects both the first phase of blood coagulation (prothrombin formation) and the second phase (thrombin formation), was within 68.47 ± 13.2% and 62.35 ± 2.78% in the first and second groups, respectively. This indicated no pronounced hypocoagulation. In the third and fourth groups, this indicator was 70.39 ± 15.29% and 69.5 ± 13.36%, respectively, indicating moderate hypocoagulation.

Data on indicators of prothrombin time, prothrombin index and INR are shown in Table 2.

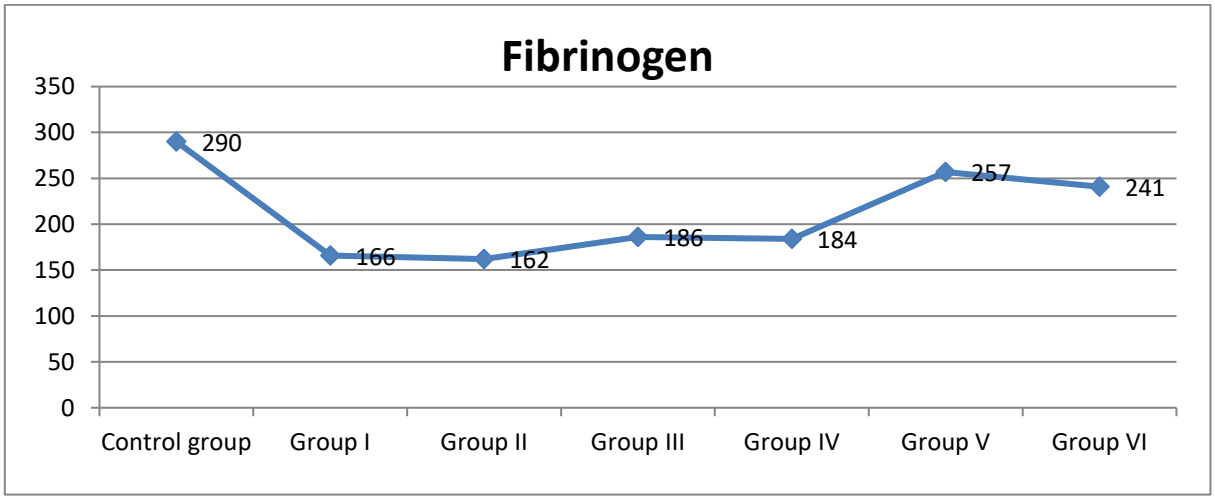
Table 2. Assessment of the second phase of blood coagulation in liver cirrhosis and chronic hepatitis of viral etiology

Groups	PT, sec	PTI, %	INR
Control groupn=20	15.57 ± 1.03*	95.6 ± 11.79*	1.03 ± 0.07*
Group I , n=30	19.68 ±3.01*	68.47 ± 13.2*	5.64±1.18*
Group II, n=30	20.93 ± 0.75*	62.35± 2.78 *	1.52 ± 0.08*
Group III, n=20	18.89 ± 2.84*	70.39 ± 15.29*	1.35 ± 0.21*
Group IV, n=20	19.61 ± 2.29*	69.5 ± 13.36*	1.39 ± 0.21*
Group V, n=21	15.55 ± 1.61 *	93.57 ± 16.94 *	1.07 ± 0.14 *
Group VI, n=20	15.54 ± 1.52*	96.05 ± 13.45*	1.04 ± 0.11*

Note: *- $p < 0.05$ significantly in relation to the control group.

To characterize the third phase of blood coagulation, the amount of fibrinogen, plasma tolerance to heparin, thrombotest and thrombin time were determined.

Fibrinogen is a coagulation factor I, a stable globulin protein and is synthesized mainly in the liver. So the study of fibrinogen indicates a clearly pronounced hypocoagulation. This is evidenced by a significant decrease in the concentration of plasma fibrinogen in all groups with liver cirrhosis of viral etiology and more decreased in groups I and II, while in groups III and IV these changes were not pronounced. In groups V and VI, fibrinogen values were similar to those in the control group.



Thrombin time is the time required for the formation of a fibrin clot in plasma when thrombin is added to it. It depends on the concentration of fibrinogen and the activity of thrombin inhibitors (antithrombin III, heparin); used to evaluate both the third phase of blood coagulation and the state of natural and pathological anticoagulants. The study of the third phase of the plasma-coagulation link of hemostasis showed that in patients of groups I, II, III and IV,

compared with the control group, there is a distinct prolongation of thrombin time. In patients with chronic viral hepatitis B and C, these indicators corresponded to those in the control group. Plasma tolerance to heparin characterizes the state of the blood coagulation system as a whole, at the same time it is an indirect indicator of the state of thrombin. The decrease in TPG depends on factors V, VIII, IX, XII. Similar changes were found in the previous analysis: in patients of groups I, II, III and IV, compared with the control group, there is a distinct decrease in plasma tolerance to heparin. In patients with chronic viral hepatitis B and C, these indicators corresponded to those in the control group.

Thrombotest is determined by the intensity of fibrin clot formation. Grade III is characterized by the inferiority of the loose clot, Grade IV the clot is formed and glued to the wall of the test tube, Grade V the clot fills the entire volume of the test tube. The main part of the thrombotest indicators were grade III in patients with liver cirrhosis, and in patients with chronic viral hepatitis B and C, these indicators were normal.

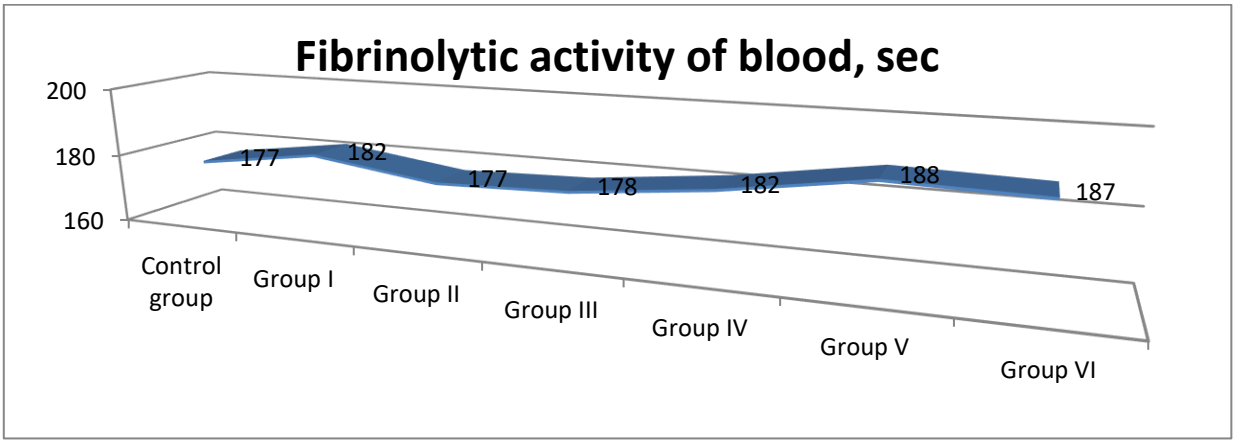
Indicators of thrombin time, plasma tolerance to heparin and thrombotest are shown in Table 3.

Table 3. Indicators of the third phase of plasma hemostasis in patients with liver cirrhosis and chronic viral hepatitis.

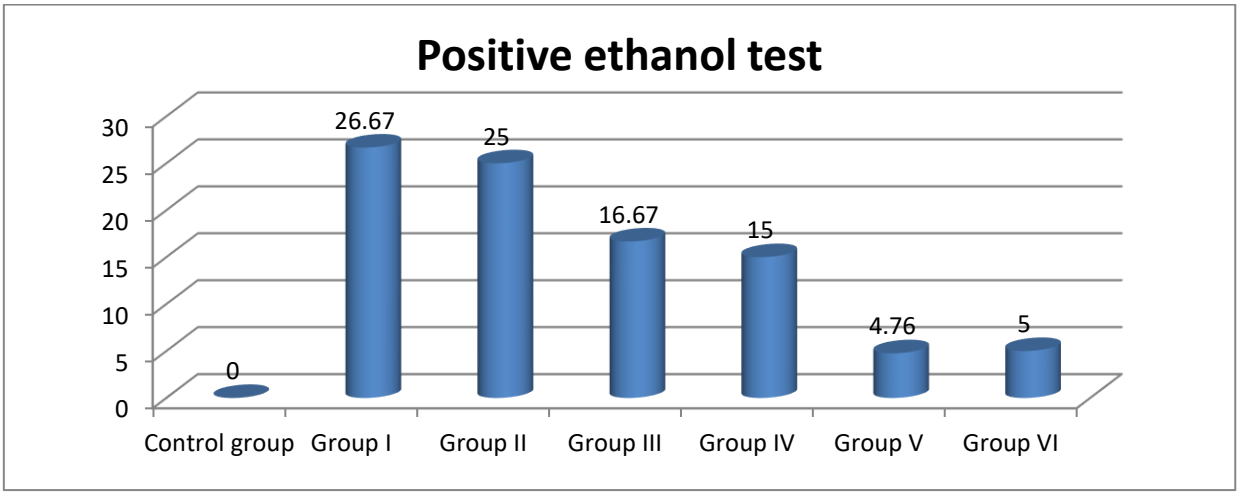
Indicators	Cotrolgroup	Group I	Group II	Group III	Group IV	Group V	Group VI
TV, sec	26.75 ± 1.67*	37.03 ± 4.52*	37.6 ± 4.84*	37.73 ± 3.28*	36.31 ± 1.56*	28.41 ± 2.44*	27.75 ± 1.92*
TPG, sec	310.05 ± 35.36*	544.37 ± 40.93*	550.3 ± 36.25*	537.95 ± 23.93*	533.56 ± 36.98*	313.38 ± 39.21*	344.4 ± 31.89*
TT	4.8 ± 0.10*	3.07 ± 0.28*	3.05 ± 0.50*	3.23 ± 0.83*	3.56 ± 0.43*	4.67 ± 0.47*	4.6 ± 0.46*

Note: *- $p < 0.05$ significantly in relation to the control group.

Another test that characterizes the state of plasma-coagulation hemostasis is the fibrinolytic activity of the blood. The clot formed as a result of blood coagulation undergoes further lysis and characterizes the fibrinolytic system. In our study, this indicator in the groups of patients did not have significant differences.



The ethanol test we conducted was positive in 8 (26.67%) patients of group I, in 5 (25.0%) patients of group II, in 5 (16.67%) patients of group III, in 3 (15%) patients of group IV group, in 1 (4.76%) patient of group V and in 1 (5%) patient of group VI after bleeding, possibly due to local intravascular coagulation, accompanied by lysis of the resulting fibrin.



Thus, our study of the indicators of the plasma-coagulation link of the hemostasis system in patients with viral etiology liver cirrhosis showed the presence of significant deviations towards the hypocoagulation shift. This was manifested by a prolongation of the blood clotting time, active partial thromboplastin time, prothrombin time, INR, plasma heparin tolerance and thrombin time, a decrease in the amount of fibrinogen, the degree of thrombotest, prothrombin index. Taking into account that APTT is prolonged in deficiency of factors XII, XI, IX and VIII, it can be assumed that the formation of these factors in patients with liver cirrhosis is impaired. It should be noted that the decrease in the activity of the blood coagulation system was more pronounced compared to the control group, mainly in the first and second groups of patients, while hypocoagulation was insignificant in the third and fourth groups. Patients with chronic viral hepatitis B and C had no abnormalities in the coagulation link of hemostasis.

FINDINGS

1. In cirrhosis of viral etiology, the state of plasma-coagulation hemostasis deviates significantly towards hypocoagulation. This is manifested by a decrease in the concentration of plasma coagulation factors (fibrinogen, prothrombin), prothrombin index, and an increase in APTT, CT, prothrombin time, INR and thrombin time.
2. The decrease in the activity of the blood coagulation system is more pronounced in the group of patients with cirrhosis of viral etiology, in contrast to cirrhosis of non-viral etiology.

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