Article

The Relationship of Disorders in the Hemostasis System with Changes in Homeostasis in Conditions of Progressive Inflammation

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Abstract: The urgency of the problem of acute peritonitis in surgical practice is due to the annual increase in morbidity, a high number of complications, therapeutic complexity and mortality. **Materials and methods**. The material of the study was 45 patients with acute peritonitis, who were divided into 3 groups depending on the course of pathology after surgery. The first group (n=15) – without complications, the second (n=15) – with wound complications, the third (n=15) – with tertiary peritonitis and sepsis. In addition to standard research methods, a number of laboratory tests are included to determine the severity of intoxication, oxidative activity, the state of the blood coagulation system, and the functional state of the liver. The study period is the 1st, 5th, 10th postoperative day. **Results**. The results showed that in the early period after surgery in patients with acute peritonitis, the state of hypercoagulemia, inhibition of fibrinolysis correlate with lipid peroxidation, endogenous intoxication, and violation of the functional status of the liver. With effective therapy, during the early postoperative period, the state of the hemostasis system and homeostasis indicators are corrected against the background of restoration of the functional status of the liver. With the aggravation of the phenomena of inflammation in the early postoperative period and the development of complications, there is a progression of changes in the studied indicators of homeostasis and hemostasis with further inhibition of the functional state of the liver. With the development of tertiary peritonitis and sepsis, the hemostasis system is modified in the form of hypocoagulemia and activation of fibrinolysis against the background of a sharp increase in endogenous intoxication, lipid peroxidation and greater inhibition of the functional status of the liver, including from its hemostasis-regulating component. **Conclusions**. The obtained results indicate the presence of a reliable correlation of disorders in the hemostasis system with changes in homeostasis in conditions of progressive inflammation.

Keywords: Peritonitis, liver, intoxication, lipoperoxidation, hemostasis.

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1. Introduction

By now acute peritonitis (AP) is considered one of the most life-threatening pathologies in emergency surgery. The relevance of AP lies in the high prevalence, polyetiology, complexity of the pathogenetic process, rapid progression, high mortality [1].

According to the literature, the death rate in acute peritonitis is 5–15%. However, with the progression of AP and the formation of complications (sepsis, shock), the mortality rate reaches 96–100 % [2].

Undoubtedly, the main reason for the decrease in the effectiveness of AP treatment seems to be insufficient knowledge of the mechanisms of its pathogenesis. Much attention has been paid to this issue recently. It was revealed that the basis of AP is: bacterial translocation, the development of endogenous intoxication, activation of proinflammatory cytokines, enteral distress syndrome,

vascular and hemostatic disorders (activation of platelet aggregation, increased vascular permeability, tissue hypoxia), the development of disseminated intravascular coagulation, etc. This can lead to multiple organ failure and death of patients [3, 4]. Modern data obtained by conducting in-depth studies have revealed a number of new pathogenetic mechanisms of the disease [5].

It should be noted that so far there has not been a significant breakthrough in understanding the role of the hemostasis system in the progression of the disease and homeostasis disorders in acute peritonitis. Therefore, the scientific search for an in-depth study of the pathogenesis of the disease with an emphasis on key mechanisms continues [6].

The purpose of the study. To establish the relationship of disorders in the hemostasis system with homeostatic modifications and the functional status of the liver with progressive acute inflammation.

2. Patients and Methods

2.1. General characteristics of patients

A clinical and laboratory study of 45 patients with acute peritonitis was conducted. The scientific work was carried out according to the ethical aspects of clinical research.

Inclusion criteria: clinical, laboratory and instrumental confirmation of the diagnosis; gender – female and male; age – 20 – 60 years; mild comorbidities; treatment – surgical.

Exclusion criteria: age – younger than 20 and older than 60 years; presence of severe concomitant diseases (infectious, oncological, somatic, mental).

The examined patients were divided into 3 groups depending on the course of pathology after surgical therapy. The first group (n=15) was without complications, the average age was 50.3±2.47 years, there were 9 men (60.0%) and 6 women (40.0%). The second (n=15) was with wound complications, the age was 60.5±3.81 years, there were 8 men (53.3%), and 7 women (46.7%). The third (n=15) – with tertiary peritonitis and sepsis, age – 66.8±3.72 years, men – 10 (66.7%), women - 5 (33.3%).

Causes of acute peritonitis: perforated appendicitis (12 (26.7%)), perforated gastric and duodenal ulcer (11 (24.4%)), perforated cholecystitis (5 (11.1%)), acute intestinal obstruction (13 (28.8%)), strangulated hernia (4 (8.9 %)).

Surgical intervention was performed for patients upon admission to the clinic and after preoperative preparation. It consisted in laparotomy, elimination of the cause of pathology, sanitation and drainage of the abdominal cavity and intestinal decompression (according to indications).

In the period before and after surgical treatment, patients were prescribed therapy, which was carried out according to clinical recommendations, which included antibacterial agents, infusion drugs, antispasmodics, painkillers, antihistamines, etc.

The study included relatively healthy people (n=15) of both sexes, aged 22-55 years.

2.2. Research methods.

Assessment of the severity of patients on the APACHE-II scale and the Mannheim Peritoneal Index (MPI). In addition to standard research methods, a number of biochemical analyses are included to determine toxemia (by the content of medium-weight molecules (MWM 280), toxicity index (TI)), oxidative stress (by the level of malondialdehyde (MDA) and diene (DC) conjugates), the state of the coagulation system (by the magnitude of the parameters of thromboelastography (TEG® 5000 Thrombelastograph® (USA)): reaction time (R), coagulation index (Cl)), liver function (by activity of alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT))in blood serum). The duration of the study is the 1st, 5th, 10th postoperative day.

2.3. Statistical analysis.

Statistical processing of the results was performed using Microsoft Office 2013, Excel Office 2013 and IBM SPSS Statistics 22 programs and using the Kraskel-Wallis and Fisher criterion.

3. Results

3.1. Analysis of indicators of endogenous intoxication.

Judging by the values of laboratory parameters, it has been recorded that patients with acute peritonitis develop endogenous intoxication syndrome.

In the first group, the content of MWM and the level of TI exceeded the normal level on the first day by 45.9 and 64.2% ($p<0.05$). On the next (5th) day after surgery against the background of drug therapy, the value of these parameters significantly decreased, but it exceeded the norm by 23.4 and 31.3% ($p<0.05$). By the final (10th) days, the level of molecules of average mass and the toxicity index for albumin were closely approaching the reference level (Fig. 1).

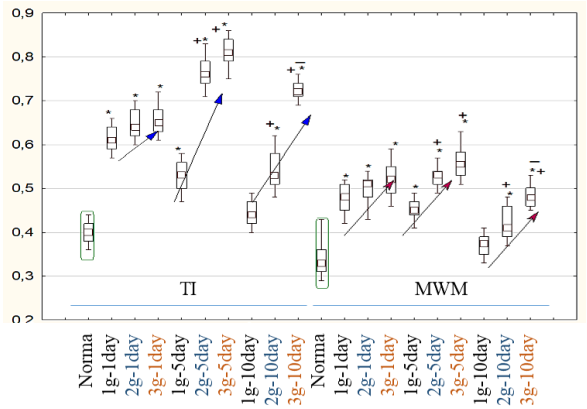

Figure 1. Dynamics of intoxication parameters. Notes here and further: * – statistically significant difference to the norm ($p<0.05$). + – statistically significant difference to the 1st group ($p<0.05$); - - statistically significant difference to the 2nd group ($p<0.05$).

In the second group, the indicators of endogenous intoxication (MWM and TI) exceeded the reference value on the first postoperative day by 49.5 and 68.7% ($p<0.05$), respectively. On the fifth day, there was an increase in the content of MWM and the level of TI, the value of which exceeded the norm by 55.3 and 74.3% ($p<0.05$), respectively. At the next stage of the follow-up period, the parameters of toxemia decreased significantly, but were higher than normal by 23.7 and 34.1% ($p<0.05$).

When analyzing the data of patients of the third group, it was found that the severity of intoxication was recorded to a high degree for all periods of the study: MWM – by 70.5 – 49.6% ($p<0.05$), TI – by 68.5 – 79.3% ($p<0.05$).

3.2. Analysis of indicators of oxidative stress.

The study of laboratory studies showed that the development of acute peritonitis is accompanied by pronounced phenomena of oxidative stress (Fig. 2).

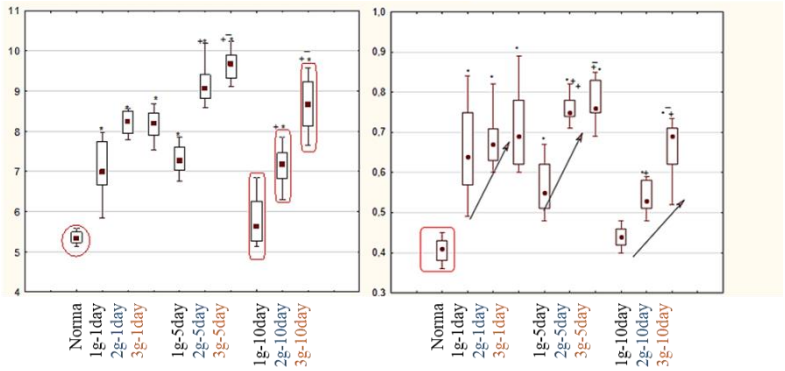

Figure 2. Dynamics of parameters of lipid peroxidation (right – MDA, left – DC).

It was demonstrated that in patients of the first group (without complications), the level of primary (DC) and secondary (MDA) lipid peroxidation products in the early stages (1st postoperative day) exceeded the norm by 63.5 and 50.0% ($p<0.05$), respectively. On the 5th day of the postoperative period, the content of DC and MDA against the background of drug postoperative support significantly decreased. Their value exceeded the norm group by 32.7 and 28.2% ($p<0.05$), respectively. 10 days after the operation, the values of the studied parameters of the floor closely approached the norm (Fig. 2).

When analyzing the activity of lipoperioxidation processes in the second and third groups, it was found that the plasma content of lipid peroxidation products was high at the first stage of observation: diene conjugates – by 65.8 and 68.0% ($p<0.05$), malonic dialdehyde – by 51.8 and 52.6% ($p<0.05$). At the second stage, the prolongation of lipid peroxidation (LPO) activity was recorded. The values of the indicators exceeded the norm. Thus, the content of DC increased by 75.3 and 68.2% ($p<0.05$), MDA – by 83.1 and 74.4% ($p<0.05$), respectively.

At the final stage of the study in the second group, the level of LPO metabolites decreased significantly, although the DC content in blood plasma exceeded the normal level by 17.9% ($p<0.05$,

and MDA – by 14.8% (p<0.05)). In the third group during this period, the level of DC and MDA remained high and exceeded the norm by 35.8 and 26.4%, respectively (Fig. 2).

3.3. Analysis of indicators of hepatic function.

Analysis of hepatic parameters in the dynamics of pathology showed the development of significant changes in the functional activity of the organ (Fig. 3).

It was found that the development of acute peritonitis in the early stages was characterized by hepatic dysfunction (Fig. 3). Thus, on the 1st day after surgical treatment, patients of the first group showed an increase in the activity of alanine aminotransferase and gamma-glutamyltransferase by 47.6 and 41.8% (p<0.05), respectively. After 5 days, a significant decrease in ALT and GGT activity was noted. However, their plasma activity exceeded the norm by 30.3 and 40.2% (p<0.05). At the final stage of the study (the 10th day after surgery), the activity of liver enzymes came close to the reference level (Fig. 3).

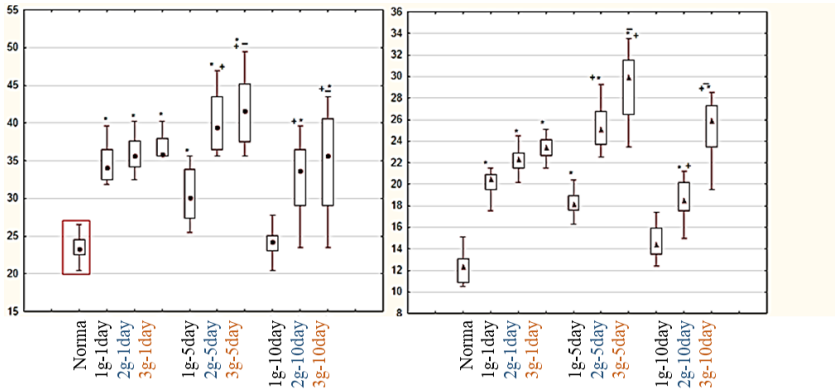

Figure 3. Dynamics of the parameters of the functions of the liver (right – GGT, left – ALT).

Patients in the second group demonstrated high activation of liver tests on the 1st and 5th days after surgery. This was evidenced by the increase in serum concentrations of ALT and GGT above the norm by 55.4 and 47.2% (p<0.05) at the first and 64.9 and 56.5% (p<0.05), respectively, at the second stage of the study. By the 9th day of observation, the activity of alanine aminotransferase and gamma-glutamyltransferase significantly decreased, but exceeded the norm by 25.6 and 19.2% (p<0.05).

In the third group, signs of hepatic depression remained at a high level at all stages of the study: on the 1st postoperative day by 56.7 and 48.1% (p<0.05), on the 5th - by 80.6 and 72.4% (p<0.05), and on the 10th – by 42.3 and 39.5% (p<0.05), respectively.

3.4. Analysis of indicators of hemostasis system.

In acute inflammation of the peritoneum, we found significant changes in the hemostasis system.

Thus, according to the TAG data, in patients of the first group (without complications), the phenomena of hypercoagulation and a decrease in fibrinolytic activity of the blood were recorded: on the first day, a decrease in R by 30.1% (p<0.05) and an elongation of Cl by 37.5% (p<0.05); after 5 days, the reaction time was below the normal level by 19.5 % (p<0.05), and the coagulation index increased by 24.1% (p<0.05). By the 10th day, coagulation and fibrinolytic activity of the blood was approaching normal (Fig. 4).

In the second group, hypercoagulation and hypofibrinolytic blood activity persisted on the first and fifth postoperative days: the R value was shortened by 40.1 and 48.9% (p<0.05), respectively, and Cl was lengthened by 33.7 and 35.1% (p<0.05), respectively. On the last day of the study, a significant restoration of the functional activity of the hemostasis system was recorded. However, the time R remained below the reference level by 21.1% (p<0.05), and the time of the coagulation index was longer by 26.9% (p<0.05).

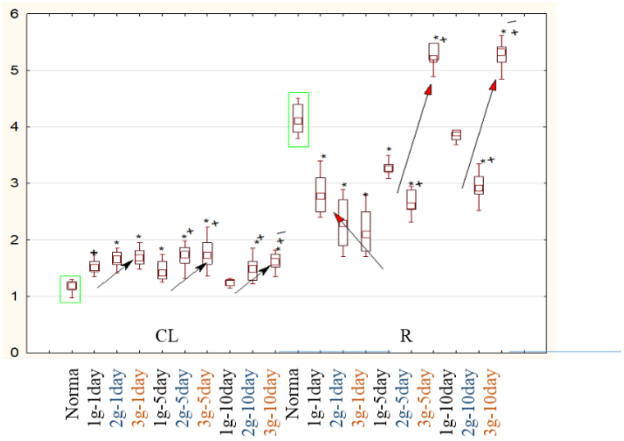

Figure 4. Dynamics of parameters of the hemostasis system.

In the third group, changes in the activity of the blood coagulation system in the form of hypercoagulation and hypofibrnolysis were detected on the first day. Thus, the R was crushed by 41.3%, and the Cl was lengthened by 52.6%. On the 5th and 10th days, the occurrence of significant changes in blood coagulation ability was demonstrated: the R exceeded the norm by 23.6 and 21.4% ($p<0.05$); the Cl became shorter by 70.1 and 56.7% ($p<0.05$), respectively.

3.5. Analysis of severity assessment.

In the course of the study, it was revealed that the severity of the studied patients, determined by the APACHE II scale, changed significantly. In patients of the first group, the number of points a day after surgery was 15.6±0.56, which corresponded to a severe degree [7]. On the fifth day, their number decreased to 8.2± 0.34, (moderate degree), on the tenth – to 4.3± 0.12 (mild degree).

In the second group, the number of points on the first day was high, and then gradually decreased, amounting to 15.9±0.74, 17.6±0.69 and 9.8±0.24, respectively, at the stages of the observation period. In the third group, the severe condition of patients persisted at all stages of the follow-up period: the number of points was 16.1±0.87, 18.2±0.94 and 13.5±0.43, respectively (Fig. 5).

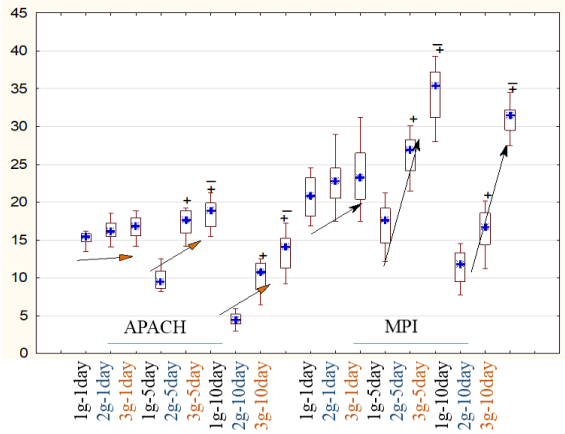

Figure 5. Dynamics of ARASNE II and MPI results.

The results of forecasting peritonitis according to the Mannheim peritoneal index showed that in the first group on the first day it was 20.4± 1.97, on the fifth – 15.6± 0.56 and on the tenth – 11.8± 0.34 (first degree of severity [8]). In the second group, the second degree of severity was recorded at the first two stages - 23.7 ±2.78 and 26.1±2.94. By the 10th day after surgery, the value of the Mannheim index decreased to 16.7±0.75. In the third group, the severity assessment on this scale showed that after the 1st day the number of points was 27.4±2.41 (second degree) and on the 5th and 10th days - 35.4±3.92 and 31.7±2.85, respectively (third degree).

When analyzing the results of surgical treatment of patients with acute peritonitis and the risk of postoperative complications, it was found that the development of postoperative negative consequences was not detected among the patients of the first group. In the second group, the formation of wound complications was noted, while three developed deep vein thrombosis of the lower limb. The latter were operated with a favorable outcome. In the third group, the observation showed the development of fatal complications: 3 had tertiary peritonitis, and 2 had sepsis. Two patients of this group died.

4. Discussion

According to modern concepts, it is shown that one of the main manifestations of disorders of the functional activity of the homeostasis system in the early stages of acute peritonitis is endotoxicosis. The latter is accompanied by the accumulation of intermediate and final toxins in the tissues and important organs (liver, kidneys, brain, etc.) of the body, leading to their functional changes [9].

In acute peritonitis, significant oxidative stress phenomena occur. A high level of toxemia, activation of lipoperoxidation processes lead to damage to various organs and systems of the body, especially the liver [10].

There is evidence that the development of dysfunction of various organs, especially the liver, in the early stages of acute peritonitis leads to a violation of the state of the blood coagulation system, which, in turn, may be a factor in the progression of the disease, the development of complications and mortality [11].

The results of the study confirmed the above. It has been established that the development of acute peritonitis is accompanied by the formation of pronounced endotoxemia, activation of lipid-modifying processes and oxidative stress, leading to serious violations of the functional status of the liver. This was accompanied by significant changes in coagulation and fibrinolytic activity of the blood. In patients of the first group, the registered changes in homeostasis indicators were reversible and were accompanied by transient phenomena of hypercoagulation and hypofibrinolysis. Moreover, by the final stage of the observation period, the state of the blood coagulation system was restored. In the second group, whose patients had various kinds of wound complications in the early postoperative period, significant violations of homeostasis persisted until 5 days after surgery, and by the 10th day there was a significant positive dynamics in their recovery. In this group, significant phenomena of hypercoagulation and inhibition of fibrinolysis were recorded in the first 5 days.. In the third group, in whose patients the progression of the disease with the formation of sepsis and tertiary peritonitis was noted, significant phenomena of intoxication, oxidative stress and liver failure were recorded during the entire follow-up period. At the same time, the state of the hemostasis system was characterized by paradoxical transformations: hypercoagulation and hypofibrinolysis – on the first day, and hypocoagulation and hypofibrinolysis – on the 5th and 10th days.

5. Conclusions

In acute peritonitis, the phenomena of hypercoagulemia, inhibition of fibrinolysis correlate with the phenomena of oxidative stress ($r=0.762-0.911$, $p<0.05$), endogenous intoxication ($r=0.812-0.955$, $p<0.05$) and impaired liver functional status ($r=0.785-0.908$, $p<0.05$). With effective therapy and improvement of the clinical and laboratory condition of patients, correction of homeostatic parameters, including hemostasis, is noted against the background of restoration of the functional status of the liver.

During the aggravation of the phenomena of peritoneal inflammation and the development of complications in the early postoperative period, there is a progression of changes in the studied indicators of homeostasis and hemostasis against the background of maintaining the depressed functional state of the liver.

With the development of tertiary peritonitis and sepsis, the hemostasis system is modified in the form of hypocoagulemia and activation of fibrinolysis against the background of a sharp increase in endogenous intoxication, oxidative stress and greater inhibition of the functional status of the liver, including from its hemostasis-regulating component.

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