Translated by E.V. Trushina

Research Article

https://doi.org/10.23934/2223-9022-2023-12-4-538-545

Diagnosis and Treatment of Manifestations of Endothelial Dysfunction in ICU Patients with Severe Acute Pancreatitis

V.V. Kiselev ✉, ***M.S. Zhigalova, S.S. Petrikov, E.V. Klychnikova, P.A. Yartsev***

Department of Emergency Surgery
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, B. Sukharevskaya Sq., 129090 Moscow, Russian Federation

✉ **Contacts:** Vladimir V. Kiselev, Candidate of Medical Sciences, Leading Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: kiselevvv@sklif.mos.ru

BACKGROUND Acute pancreatitis is an aseptic inflammation of the demarcation type based on necrosis of pancreatic acinar cells, and enzymatic aggression, followed by expanding necrosis and dystrophy of the gland, in which damage to surrounding tissues, as well as distant organs and systems, and the addition of a secondary purulent infection are possible. An important pathogenetic aspect of the severe course of acute pancreatitis is endothelial dysfunction. The latter often begins as a diffuse activation of coagulation, which further potentiates the progression of the systemic inflammatory response syndrome and, thereby, complicates the course of acute pancreatitis. There is a connection between the activation of coagulation and the severity of inflammation. Traumatic tissue injury, followed by hypoperfusion, hemodilution, hypothermia, and acidosis cause acute post-traumatic coagulopathy. The inflammatory process activates the coagulation system, reduces the activity of natural anticoagulants and disrupts the functioning of the fibrinolytic system, thereby leading to thrombosis.

AIM OF STUDY Improving the results of treatment of patients with severe acute pancreatitis by choosing the optimal method of extracorporeal hemocorrection and anticoagulant therapy.

MATERIAL AND METHODS The present retrospective-prospective study included 76 patients (50 (65.7%) men and 26 (34.2%) women) diagnosed with severe acute pancreatitis. To assess the effectiveness of the therapy, the patients were divided into 2 groups: the control group (n=34), based on the retrospective analysis of case histories, included patients who received standard conservative therapy. The severity of the condition was assessed using APACHE II, SOFA, MARSHALL and Ranson scales, and amounted to 16.8±4.2, 3.44±1.32, 2.6±0.64, 3.8±0.52 points, respectively. The main group (n=42) included patients whose treatment was supplemented with the use of low molecular weight heparin preparations, extracorporeal methods of hemocorrection with the inclusion of cytokine adsorption together with renal replacement therapy. The severity of the condition of the 2nd group's patients was assessed using APACHE II, SOFA, MARSHALL and Ranson scales, and amounted to 16.6±3.4, 3.26±1.24, 2.5±0.72, 3.6± 0.48 points, respectively.

CONCLUSION As a result of expanded therapeutic tactics for severe acute pancreatitis (SAP) using sorption methods of extracorporeal hemocorrection, anticoagulant therapy with low molecular weight heparin, as well as the inclusion of saline enteral solution in the therapeutic regimen to restore intestinal propulsive function, it was possible to reduce the number of purulent-septic complications by 1.6 times, cases of development of multiple organ failure by 1.5 times, and mortality by 1.7 times.

Keywords: acute pancreatitis, endothelial dysfunction, systemic inflammatory response syndrome, coagulation activation
For citation Kiselev VV, Zhigalova MS, Petrikov SS, Klychnikova EV, Yartsev PA. Diagnosis and Treatment of Manifestations of Endothelial Dysfunction in ICU Patients with Severe Acute Pancreatitis. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2023;12(4):538–545. https://doi.org/10.23934/2223-9022-2023-12-4-538-545 (in Russ.)
Conflict of interest Author declare lack of the conflicts of interests
Acknowledgments, sponsorship The study has no sponsorship

Affiliations

Vladimir V. Kiselev	Candidate of Medical Sciences, Leading Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-0170-7775, kiselevvv@sklif.mos.ru; 35%, development of the study's concept and design, analysis of data obtained, text editing
Maria S. Zhigalova	Candidate of Medical Sciences, Researcher, Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-4520-1124, zhigalovams@sklif.mos.ru; 30%, development of the study's concept and design, analysis of data obtained, text preparation and editing
Sergey S. Petrikov	Corresponding Member of the Russian Academy of Sciences, Professor, Doctor of Medical Sciences, Director, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-3292-8789, petrikovss@sklif.mos.ru; 15%, development of the study's concept and design, analysis of data obtained, text editing

Elena V. Klychnikova	Candidate of Medical Sciences, Head, Clinical and Biochemical Laboratory of Emergency Research Methods, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-3349-0451, klychnikovaev@sklif.mos.ru; 10%, development of the study's concept and design, analysis of data obtained, text editing
Petr A. Yartsev	Doctor of Medical Sciences, Professor, Head, Scientific Department of Emergency Surgery, Endoscopy and Intensive Care, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0003-1270-5414, yartsevpa@sklif.mos.ru; 10%, development of the study's concept and design, analysis of data obtained, text editing

AP — acute pancreatitis
APTT — activated partial thromboplastin time
ATIII — antithrombin III
CRP — C-reactive protein
FG — fibrinogen
IL-6 — interleukin-6
LMWH — low molecular weight heparin
MOF — multiple organ failure
PA — plasmapheresis
PCT — procalcitonin
SAP — severe acute pancreatitis
SIRS — systemic inflammatory response syndrome
RRT — renal replacement therapy

INTRODUCTION

Acute pancreatitis (AP) is an aseptic inflammation of the demarcation type, which is based on necrosis of acinar cells of the pancreas and enzymatic aggression, followed by expanding necrosis and degeneration of the gland, in which damage to surrounding tissues, as well as distant organs and systems, and the addition of a secondary purulent infection are possible [1]. The interaction between coagulation activation and inflammation is based on positive feedback [2].

In the Russian Federation, 155,567 people were hospitalized with a diagnosis of AP in 2017; 153,331 people were hospitalized in 2018. 4234 patients (2.7%) died in 2017, and 4231 (2.8%) in 2018. 17,352 patients (11.2%) underwent surgery in 2017; and 20,176 (13.2%) in 2018. Postoperative mortality was 15.4% and 13.0%, respectively. Among acute diseases of the abdominal organs, acute pancreatitis ranks third after acute appendicitis and acute cholecystitis [3]. According to the literature, the current incidence rate in the world is 13–45 cases per 100,000 adults [4]. The incidence rate in the United States is 50–80 cases per 1 million adults per year [5]. In the Russian Federation, the incidence rate ranges from 27 to 50 cases per 1 million adults per year [6]. It is worth noting that AP and its complications lead to significant socio-economic losses, which in developed countries amount to billions of dollars per year, since the majority of patients are people of working age [3, 4].

An important pathogenetic aspect of severe acute pancreatitis (SAP) is endothelial dysfunction. The latter often begins as diffuse activation of coagulation, which further significantly potentiates the progression of systemic inflammatory response syndrome (SIRS), thereby complicating the course of AP [2,7,8].

According to performed research, in the early phase of acute pancreatitis there is a decrease in the number of platelets and their increased activation, a decrease in the concentration of natural anticoagulants, secondary activation of fibrinolysis, and an increase in the concentration of fibrin breakdown products, which correlate with the values of inflammatory markers and the severity of AP [9].

In severe cases of AP, classical factors of Virchow's triad occur, mediating procoagulant changes in blood components, increased permeability of the vascular wall and decreased blood flow velocity, predisposing to the development of thrombotic complications [10, 11]. An increased concentration of prothrombin, fibrinogen and D-dimer, a decrease in the concentration of protein C, antithrombin III, plasminogen and activated partial thromboplastin time (aPTT), elevated levels of plasminogen activator inhibitor in the first 24 hours from the onset of abdominal pain syndrome were associated with the development of organ dysfunction. Moreover, an increase in the level of D-dimer and fibrinogen in the first day from the onset of the disease is directly related to the risk of high mortality in patients with SAP [10, 12, 13].

The interaction between coagulation activation and inflammation is based on positive feedback. Hypoperfusion, hemodilution, hypothermia, and acidosis cause acute coagulopathy. The inflammatory process activates the coagulation system, reduces the activity of natural anticoagulants and disrupts the functioning of the

fibrinolysis system, thereby leading to thrombotic complications [12, 14, 15]. One of the manifestations of SIRS is damage to the vascular endothelium, which cells synthesize a large number of biologically active substances playing an important role in many processes in normal and pathological conditions (state of hemodynamics, hemostasis, immune reactions, regeneration, etc.). There is a relationship between the mechanisms of inflammation, coagulation and endothelial cell dysfunction with pathophysiological reactions that contribute to the generalization of the infectious process, which leads to a severe complication of acute pancreatitis - organ dysfunction. SIRS involves systemic activation of both the coagulation and fibrinolytic systems, which ultimately leads to microvascular thrombosis and organ dysfunction [15, 16].

The direct relationship between haemostatic abnormalities and the development of SIRS is the reason for anticoagulant therapy and extracorporeal blood treatment for patients with AP. The National Clinical Guidelines, without clear specification, indicate disaggregant antithrombotic therapy, and list plasmapheresis (PA) and hemofiltration as extracorporeal treatment methods. However, PA is often associated with the development of hypoalbuminemia, which requires repeated intravenous infusion of an expensive albumin solution. According to the literature, performing PA in the acute phase of AP often leads to the development of purulent-septic complications in the future, which is associated with the indiscriminate elimination of humoral immune factors [17, 18].

All of the above served as the basis for conducting this research, which will allow choosing the optimal anticoagulant and extracorporeal therapy.

Aim: to improve the treatment outcomes of patients with SAP by choosing the optimal method of extracorporeal hemocorrection and anticoagulant therapy.

MATERIAL AND METHODS

The present retrospective-prospective study included 76 patients (50 (65.7%) males and 26 (34.2%) females) diagnosed with SAP. The mean age was 52.6±12.4 years.

Inclusion criteria:

1. Admission to the intensive care unit (ICU) 24–72 hours after the onset of abdominal pain syndrome.
2. Diagnosis of SAP.
3. Age 18–80 years.
4. APACHE II score of more than 10.
5. SOFA score of more than 2.
6. The severity of intestinal failure syndrome (IFS) is at least grade 2.

Exclusion criteria:

1. The agonal state of the patient.
2. Unstable hemodynamics (increasing dosages of vasopressor and inotropic support).
3. The presence of competing diseases that determine the severity of the condition.
4. History of long-term use of anticoagulants.
5. Presence of cancer.
6. Presence of autoimmune diseases.
7. Severe liver dysfunction.
8. Injuries or surgical interventions in the central nervous system, organs of vision and hearing.
9. Development of disseminated intravascular coagulation (DIC) syndrome as part of heparin-induced thrombocytopenia.
10. Acute bacterial endocarditis and prolonged endocarditis.
11. Organic disorders with an increased risk of bleeding (active peptic ulcer, hemorrhagic stroke, cerebral aneurysm or cerebral neoplasia).
12. Refusal of treatment.

To assess the effectiveness of the therapy, the patients were divided into two groups.

The Comparison Group (n=34), based on a retrospective analysis of the medical records, included patients with SAP who received the following standard conservative therapy: infusion (volume of 30–40 ml/kg body weight, using predominantly crystalloid solutions), antisecretory, symptomatic, antibacterial therapy (according to microbiological analysis of biological media with determination of sensitivity to antibacterial drugs), epidural analgesia, enteral support (intestinal decontamination, minimal enteral nutrition in a volume of no more than 300 ml of isocaloric nutritional mixture with an administration rate of 30 ml/hour), anticoagulant therapy using unfractionated heparin, extracorporeal

hemocorrection methods using plasmapheresis and continuous renal replacement therapy (RRT). The severity of the patients' condition was assessed using the following scales: APACHE II, SOFA, MARSHALL, and Ranson, amounting to 16.8±4.2; 3.44±1.32; 2.6±0.64; 3.8±0.52 points; respectively (Table 1).

The Main Group (n=42) included patients with SAP, whose treatment was supplemented with the use of low molecular weight heparin (LMWH) - bemiparin sodium (molecular weight of 3000–4200 Da) and combined extracorporeal methods of hemocorrection: hemoadsorption of cytokines with continuous venovenous hemodiafiltration. The severity of the patients'condition was assessed using the following scales: APACHE II, SOFA, MARSHALL, and Ranson, which amounted to 16.6±3.4; 3.26±1.24; 2.5±0.72; 3.6±0.48 points, respectively (Table 1).

Table 1

Assessment of the severity of the condition of patients with severe acute pancreatitis

Scale	Comparison Group (n=34)	Main Group (n=42)
APACHE II	16.8±4.2	16.6±3.4
SOFA	3.44±1.3	3.26±1.24
MARSHALL	2.6±0.64	2.5±0.72
Ranson	3.8±0.52	3.6±0.48

The following parameters were assessed in the patients of the both groups: aPTT, blood levels of fibrinogen (FG), D-dimer, antithrombin III (ATIII), interleukin-6 (IL-6), C-reactive protein (CRP) and procalcitonin (PCT). Examination of the state of the hemostasis system was carried out on an ACL TOP-700 automatic coagulometer (Instrumentation Laboratory, USA) using Instrumentation Laboratory (USA) reagents. The measurements were performed on the 1st, 3rd, 7th and 10th days of the patients' stay in the ICU.

All the patients were standardized by age, gender and concomitant pathology. Statistical analysis was made using Statistica 10.0 and MS Excel. For each variational series, we calculated the mean value (M), standard deviation (σ) for the values of the parametric distribution; median (Me), 25% quartile (Q1), and 75% quartile (Q3) for the values of the nonparametric distribution. To clarify the applicability of parametric tools, we assessed whether the distribution of variables was normal using the Shapiro–Wilk test. Based on the results of this analysis, it was revealed that parametric comparison criteria were not applicable. The research groups were compared with each other using the Kruskal-Wallis analysis of ranks, as well as the Mann-Whitney U test (for paired comparisons). The correlation was assessed by calculating the Spearman correlation coefficient. When assessing the statistical significance of differences and changes, $p < 0.05$ was taken as the threshold value.

RESULTS AND DISCUSSION

When assessing the results of coagulological and immunological examination (Table 2), the patients of both groups showed an increase in blood levels of FG (Fig. 1A), D-dimer (Fig. 1C), as well as pro-inflammatory markers (Fig. 1 E–G) on the 1st day. The increase in the level of these indicators reached a maximum on the 3rd day of dynamic observation. By the 7th day, a statistically significant decrease in AT III content (Fig. 1D), and an increase in the level of inflammatory markers in the patients of the Comparison Group were noteworthy. At the same time, on the 7th day of dynamic observation in the Main Group, as a result of the inclusion of sorption methods of extracorporeal hemocorrection and prevention of thrombohemorrhagic complications in complex intensive therapy, statistically significant decreases in the levels of FG (Fig. 1A), D-dimer (Fig. 1C), CRP (Fig. 2E), PCT (Fig. 2F), and IL-6 (Fig. 2G) were noted. In the patients of the Comparison Group, against the background of standard conservative therapy, a tendency towards a decrease in the level of inflammatory mediators, fibrinolysis products, and an increase in the concentration of AT III (1D) was observed only on the 10th day. Moreover, the patients of the Main Group maintained positive dynamics, which consisted of a statistically significant decrease in the levels of FG (Fig. 1A) and D-dimer (Fig. 1C); and the levels of AT III (1D) and PCT (Fig. 1F) reached normal values. There were no statistically significant changes in aPTT levels over the entire study period (Fig. 1B).

Table 2

Laboratory results in patients during treatment in dynamics, Me (Q1; Q3)

Parameter	Group	Days			
		1	3	7	10
APTT	Comparison Main	27.3 (24.3; 32.1) 30.0 (25.7; 32.8)	29.7 (24.3; 32.1) 31.4 (28.6; 34.4)	27.8 (19.3; 29.4) 28.4 (26.2; 29.4)	27.45 (26.2; 31.5) 26.3 (24.7; 28.8)
AT III	Comparison Main	89.4 (78.0; 99.6) 86.4 (76.4; 100.7)	74.2 (56.5; 87.9) 76.1 (64.6; 94.1)	72.3 (52.4; 84.6) 99.4 (92.6; 106.7) ▪♦	80.0 (74.9; 91.2) 107.2 (93.7; 11.3) *▪♦
FG	Comparison Main	4.4 (3.9; 5.1) 4.9 (4.2; 5.1)	5.8 (5.3; 6.6) 4.7 (3.1; 5.9)	5.6 (5.2; 6.8) 3.8 (2.8; 5.1) *♦	5.1 (4.9; 6.3) 2.6 (1.8; 5.2) *▪♦
D-dimer	Comparison Main	3.8 (2.5; 4.9) 3.2 (2.4; 4.7)	5.2 (3.3; 5.9)* 5.0 (3.3; 6.7)	4.9 (4.7; 6.1) 3.2 (2.1; 4.2) ▪♦	4.8 (3.1; 5.6) 1.5 (1.1; 2.1) *▪▪♦
CRP	Comparison Main	125.9 (98.4; 195.1) 129.7 (96.4; 171.0)	165.2 (130.9; 231.7)* 151 (128; 256.0)	193.9 (100.1; 280.4) *▪ 100.6 (92.4; 262.0) *▪♦	134.5 (79.9; 191.4) * 59.9 (44.9; 81.0) *▪▪♦
PCT	Comparison Main	0.6 (0.4; 1.2) 0.4 (0.3; 0.9)	1.4 (0.8; 4.7) 0.8 (0.4; 1.2)*▪	2.3 (0.3; 2.8) *▪ 0.3 (0.2; 0.4) ▪♦	2.1 (0.3; 2.2) * 0.2 (0.1; 0.4) *▪♦
IL-6	Comparison Main	78.1 (67.0; 90.3) 76.3 (67.0; 84.0)	151.8 (119.3; 199.8) * 115.7 (76.4; 175.1)*	164.9 (124.9; 187.5) * 54.9 (41.5; 101.0) *▪♦	110.1 (63.9; 120.3) * 50.1 (43.0; 54.6) *▪♦

Notes: * — p<0.05 in comparison with the original data; • — p<0.05 compared to day 3; ▪ — p<0.05 in comparison with the 7th day, ♦ — p<0.05 in relation to with the data of the comparison group. AT III - antithrombin III; APTT —activated partial thromboplastin time; PCT—procalcitonin; FG — fibrinogen; CRP — C-reactive protein; IL-6 — interleukin-6

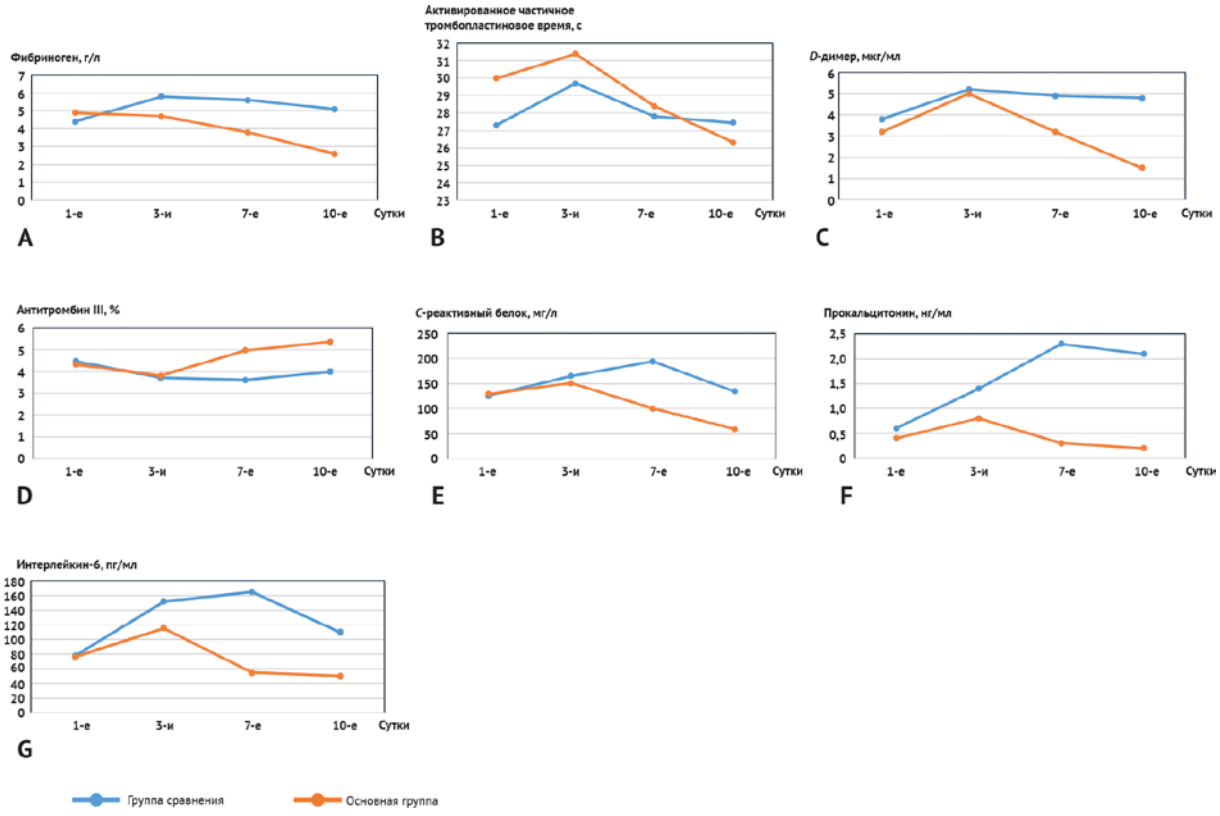

Fig. 1. Dynamics of laboratory parameters depending on the herapy type

The development of purulent-septic complications among the patients of the Comparison Group was recorded in 41.2% of cases, multiple organ failure (MOF) - in 32.3%. The mortality rate was 23.5%. As a result of extended complex therapy, the development of purulent-septic complications in the Main Group was 26.2% (p=0.17), MOF - 21.4% (p=0.28), mortality - 14.3% (p=0.3) (Fig. 2).

Fig. 2. Outcomes of treatment for SAP in the selected groups of patients

Despite the lack of statistically significant results, the data obtained indicate that the inclusion of sorption methods of extracorporeal hemocorrection and LMWH drugs for the prevention of thrombohemorrhagic complications in complex intensive therapy helps reduce the number of purulent-septic complications by 1.6 times, cases of MOF development by 1. 5 times, mortality by 1.7 times (Fig. 2).

To assess the intensity of the relationship between SIRS and the hemostatic system, the correlation between changes in hemostasis parameters and inflammatory markers was studied (Table 3).

As can be seen from the table, there is a weak correlation between changes in APTT and the concentration of inflammatory markers. A moderate correlation was established between a decrease in the level of AT III and its increase for CRP, PCT and

Table 3

Spearman's rank correlation coefficient between changes in the concentrations of coagulation parameters and proinflammatory cytokines

Parameters	Days		
	3	7	10
APTT-CRP	0.4	0.3	0.2
APTT-PCT	0.1	0.3	0.3
APTT–IL-6	0.2	0.4	0.3
ATIII–CRP	-0.4	-0.6	-0.5
ATIII–PCT	-0.4	-0.6	-0.4
ATIII–IL-6	-0.5	-0.5	-0.4
FG– CRP	0.6	0.8	0.7
FG–PCT	0.6	0.7	0.5
FG–IL-6	0.7	0.9	0.7
D-dimer – CRP	0.6	0.7	0.7
D-dimer –PCT	0.5	0.7	0.6
D-dimer –IL-6	0.7	0.9	0.7

Notes: AT III — antithrombin III; APTT — activated partial thromboplastin time; PCT — procalcitonin; FG — fibrinogen; CRP — C-reactive protein; IL-6 — interleukin-6

IL-6 on the 3rd day of dynamic observation; a noticeable correlation, consisting of an increase in the level of natural anticoagulant and a decrease in immunological parameters, was recorded on the 7th and 10th days of observation in the ICU. A noticeable correlation was observed between changes in the concentrations of FG, D-dimer, CRP and PCT on day 3, while the Spearman correlation coefficient between FG, D-dimer and an increase in IL-6 levels was assessed as high. A high correlation was noted between these indicators on the 7th day of stay in the ICU. By the 10th day, a high correlation was observed between the decrease in the levels of FG, D-dimer, levels of CRP and IL-6, a noticeable connection was noted between these indicators of hemostasis and the level of PCT.

Thus, the data obtained from statistical correlation analysis indicate a close relationship between the severity of SIRS and disorders in the hemostatic system, which likely contributes to the further development of thrombotic complications and organ dysfunction in these patients.

CONCLUSION

During the research, patients in both groups showed a statistically significant increase in the levels of FG and D-dimer in the blood, decrease in the levels of AT III, and increase in the levels of pro-inflammatory markers. A correlation was also established (Spearman coefficient 0.4–0.9) between changes in the level of parameters of the hemostatic system and markers of inflammation.

As a result of the undertaken expanded therapeutic tactics for severe acute pancreatitis using sorption methods of extracorporeal hemocorrection, anticoagulant therapy using low molecular weight heparins, as well as the inclusion of a saline enteral solution in the therapeutic regimen to restore the propulsive function of the intestine, it was possible to reduce the number of purulent-septic complications by 1.6 times, cases of multiple organ failure by 1.5 times, and mortality by 1.7 times.

FINDINGS

1. The inclusion of low molecular weight heparin in the complex therapy for SAP made it possible to statistically significantly reduce the levels of FG ($p = 0.036$) and D-dimer ($p = 0.043$) by the 7th day of observation in the ICU.
2. Cytokine adsorption methods allowed a statistically significant reduction in the level of inflammatory markers (CRP ($p=0.04$), PCT ($p <0.01$), IL-6 ($p=0.31$)) by the 7th day of stay in the ICU.
3. A high correlation was established (Spearman coefficient = 0.7) between the concentration of hemostasis indicators (FG, D-dimer) and proinflammatory cytokines in patients with SAP.

REFERENCES

1. Kiselev VV, Zhigalova MS, Klychnikova EV. Use of Low-Molecular-Weight Heparin Preparations in Patients with Acute Pancreatitis. *Hospital Medicine: Science and Practice.* 2021;4(2):9–12. (In Russ.) https://doi.org/10.34852/GM3CVKG.2021.35.47.003
2. Bagnenko SF, Krasnorogov VB, Goltsov VR. Plasmapheresis Application Opportunities in Acute Necrotizing Pancreatitis. *Annals of HPB Surgery*. 2007;12(1):15–22. (In Russ.)
3. Kiselev VV, Zhigalova MS, Klychnikova EV. The Interaction Between the Systemic Inflammatory Response and Disorders in the Hemostasis System in Patients with Acute Heavy Pancreatitis. *Hospital Medicine: Science and Practice*. 2021;4(1):10–16. (In Russ.) https://doi.org/10.34852/GM3CVKG.2021.50.48.002
4. Kolotil'shchikov AA. Vybor sposoba sekvestrektomii v lechenii bol'nykh pankreonekrozom: Cand. med. sci. diss. synopsis. Moscow; 2021. Available at: https://search.rsl.ru/ru/record/01010970175 [Accessed Nov 24, 2023]
5. Marukhov AV, Khoroshilov SE, Zakharov MV, Nikulin AV, Chubchenko NV. Extracorporeal detoxification in complex treatment of severe acute pancreatitis. *Russian Journal of Anesthesiology and Reanimatology.* 2020;(5):23–29. (In Russ.) https://doi.org/10.17116/anaesthesiology202005123
6. Novikov SV, Rogal ML. Evolution of the Classification of Severity of Acute Pancreatitis. Review. *Herald of Surgical Gastroenterology*. 2021;(2):3–11. (In Russ.)
7. Revishvili ASh, Kubyshkin VA, Zatevakhin II, Bagnenko SF, Polushin YuS, Maystrenko NA, et al. *Klinicheskie rekomendatsii. Ostryy pankreatit*. 2020. (In Russ.) Available at: http://xn----9sbdbejx7bdduahou3a5d.xn--p1ai/stranica-pravlenija/klinicheskie-rekomendaci/urgentnaja-abdominalnaja-hirurgija/ostryi-pankreatit-versija-sentjabr-2020.html [Accessed Nov 24, 2023]
8. Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. *Clin Rheumatol*. 2020;39(9):2529–2543. PMID: 32654082 https://doi.org/10.1007/s10067-020-05275-1
9. Alberts C, Alsfasser G. Severe Acute Pancreatitis – How Conservative Can We Be? *Visceral Medicine*. 2018;34(6):432–434. PMID: 30675488 https://doi.org/10.1159/000494097
10. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. *Gastroenterology*. 2020;158(1):67–75. PMID: 31479658 https://doi.org/10.1053/j.gastro.2019.07.064
11. Birkbeck R, Humm K, Cortellini S. A review of hyperfibrinolysis in cats and dogs. *J Small Anim Pract*. 2019;60(11):641–655. PMID: 31608455 https://doi.org/10.1111/jsap.13068
12. Branchford BR, Carpenter SL. The Role of Inflammation in Venous Thromboembolism. *Front Pediatr*. 2018;6:142. PMID: 29876337 https://doi.org/10.3389/fped.2018.00142
13. Dumnicka P, Maduzia D, Ceranowicz P, Olszanecki R, Drożdż R, Kuśnierz-Cabala B. The Interplay between Inflammation, Coagulation and Endothelial Injury in the Early Phase of Acute Pancreatitis: Clinical Implications. *Int J Mol Sci*. 2017;18(2):354. PMID: 28208708 https://doi.org/10.3390/ijms18020354
14. Foley JH, Conway EM. Cross Talk Pathways Between Coagulation and Inflammation. *Circ Res*. 2016;118(9):1392–1408. PMID: 27126649 https://doi.org/10.1161/CIRCRESAHA.116.306853
15. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. *Crit Care Med*. 2020;48(9):1358–1364. PMID: 32467443 https://doi.org/10.1097/CCM.0000000000004458
16. Mukhopadhyay S, Johnson TA, Duru N, Buzza MS, Pawar NR, Sarkar R, et al. Fibrinolysis and Inflammation in Venous Thrombus Resolution. *Front Immunol*. 2019;10:1348. eCollection 2019. PMID: 31258531 https://doi.org/10.3389/fimmu.2019.01348

17. Papageorgiou C, Jourdi G, Adjambri E, Walborn A, Patel P, Fareed J, et al. Disseminated Intravascular Coagulation: An Update on Pathogenesis, Diagnosis, and Therapeutic Strategies. *Clin Appl Thromb Hemost*. 2018;24(9 suppl):8S–28S. PMID: 30296833 https://doi.org/10.1177/1076029618806424
18. Patel P, Walborn A, Rondina M, Fareed J, Hoppensteadt D. Markers of Inflammation and Infection in Sepsis and Disseminated Intravascular Coagulation. *Clin Appl Thromb Hemost*. 2019;25:1076029619843338. PMID: 30991817 https://doi.org/ 10.1177/1076029619843338

Received on 09/02/2023
Review completed on 13/02/2023
Accepted on 26/09/2023