

The Comparative Characteristics of the Hemostatic System Indices in the Assessment of Late Complications of Acute Destructive Pancreatitis

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Abstract: Studies involving 125 patients were carried out to determine the level of activation of the markers of the hemostatic system and their contribution to the prevention and early diagnosis of complications in patients with acute destructive pancreatitis. Levels of D-dimer and fibrinopeptide A (FpA) were determined in patients. The APACHE II and SOFA scores were used to assess disease severity. Furthermore, studies aimed at determining the indices of the hemostatic system, pancreatic enzymes, liver function tests (ALT, AST, QGT, bilirubin and bilirubin fractions), C-reactive protein and fibrinolytic activity of blood were carried out. A significant elevation of levels of D-dimer (2000 ng/ml) and FpA (6.1 ± 1.9 2000 ng/ml) was detected in patients participating in the study. This fact suggests that acute pancreatitis results in activation of the hemostatic system and indicates excessive formation and lysis of fibrin. By analyzing the data obtained, the authors have arrived at a conclusion that the emergence and development of polyorganic insufficiency in patients with acute destructive pancreatitis is closely related to the activation of the hemostatic system. Thus, the plasma levels of FpA and D-dimer are significant diagnostic indices enabling early diagnosis and control of the disorders of the hemostatic system.

Key words: Acute Pancreatitis • Hemostatic System • D-Dimer

INTRODUCTION

Among acute surgical pathologies of a abdominal cavity; frequency of death rate from a acute pancreatitis makes 8-45 % that remains an actual problem of emergency surgery. Despite of a variety of surgical tactics and a complex of intensively medical actions, an acute pancreatitis, in view of a high mortality percentage, remains to one of heavy pathologies of abdominal surgery.

The reason is the increasing morbidity rates among patients with acute pancreatitis, which is a direct result of worsened nutrition, an increased consumption of alcohol and its surrogates, drug abuse and an unfavorable ecological situation [1-3].

Despite the achievements in the field of therapy and diagnosis of acute pancreatitis, some questions have not been solved thus far; the mortality rate still remains rather high. The recently published literature devoted to the diagnosis and therapy of acute pancreatitis has demonstrated that the progress in treatment of this

pathology has not reduced the topicality of the problem. The studies have shown that complications related to the hemostatic system are one of the reasons for such a high mortality rate. The clinicians face difficulties in the prediction of possible complications related to the hemostatic system at different stages of acute pancreatitis. Regardless of the fact that a sufficient body of data on the efficiency of drug therapy of disorders of the hemostatic system upon acute pancreatitis has been accumulated, pathogenesis, clinical manifestations and diagnosis of these changes have not been solved yet. There are still remain controversial points related to most of the important questions. The methods for the correction and monitoring of the hemostatic system indices have not been fully developed yet [2, 5-7].

It is widely believed that the development of the disseminated intravascular coagulation (DIC) syndrome is the most severe disorder of the hemostatic system in surgical patients. The development of the DIC syndrome significantly worsens prognosis of the disease. In hospitalized surgical patients, the emergence of the DIC

syndrome results from the development of disseminated purulent peritonitis and destructive pancreatitis. These diseases are accompanied by the systemic inflammatory response syndrome, sepsis and septic shock. Sepsis is typically accompanied by polyorganic insufficiency (POI) and the DIC syndrome [2, 7-10].

In overwhelming majority of cases, the DIC syndrome upon acute destructive pancreatitis is a common nonspecific disorder of the multicomponent hemostatic system and a significant reason for the development of pathological processes in the disease mechanism.

Although the clinical picture of the DIC syndrome has a number of symptoms, there are two key factors, namely, the intensity of the hemorrhagic process and disruption of microcirculation, which can cause polyorganic dysfunction. The DIC syndrome primarily manifests itself in damaging organs with intensive microcirculation, such as lungs, kidney, adrenal glands, gastrointestinal tract, brain and liver [3, 9, 11, 12].

The course of destructive pancreatitis is often complicated by polyorganic insufficiency (POI) and is thus aggravated by an increase in the probability of fatal outcome. The reasons for the emergence of POI have not been elucidated yet. Hypoxia, endogenous intoxication and the immunological conflict are the ethiological factors of POI. In many scientific works in occurrence of POI the role of infringements hemocoagulation and as its final display occurrence DIC syndrome has been confirmed. Furthermore, interesting data on the contribution of oxidative stress (OS) to the emergence of POI and its effect on the hemostatic potential have been obtained [1-6]. The information about studying the indices of fibrinogen-A and D-dimers to assess the efficacy of anticoagulant therapy and system activation can be found in studies [1, 7-10].

When considering various research studies devoted to activation of hemostatic markers and the attempts at revealing the prognostic value of the indices of FpA and D-dimer levels, one can conclude that the risk of thrombotic complications for most diseases is associated with an increase in the D-dimer level. It is highly possible that this fact is not unexpected, since the normally functioning anticoagulation system can prevent coagulation activity of thrombin to a necessary extent.

A conclusion can be drawn based on the forementioned facts that plasma concentrations of FpA and D-dimer are the key indices of activation of the human hemostatic system [3, 4, 8, 13, 14, 15].

The study was aimed at:

- Predicting the beginning of the necrotic stage of acute pancreatitis by determining the D-dimer level.
- Determining the contribution of oxidative stress to the genesis of hemocoagulation disorders in patients with acute pancreatitis.
- Determining the reasonability of using the deaggregation therapy to correct the system indices.
- Determining the efficacy of low-molecular-weight heparin for early correction of the hemostatic system indices based on the data obtained.
- Determining the contribution of intravascular coagulation to the formation of POI.

MATERIALS AND METHODS

The study was based on the results of examination and therapy of 125 patients (72 males and 53 females aged 23–75) who were admitted to the surgery and intensive reanimation departments with a diagnosis of acute pancreatitis.

All patients appealed for medical aid during 12–24 h after disease onset. Acute pancreatitis was diagnosed based on the patients' history and the data obtained by the clinical, laboratory and instrumental examination. Laparoscopic drainage of the abdominal cavity was performed in 55 patients; among them, 36 patients underwent laparotomy, cholecystostomy, drainage of the abdominal cavity and of the omental bursa. Laparotomy with sanation of the abdominal cavity and elimination of the peritonitis source was used in patients with disseminated purulent peritonitis (16 individuals). The amelioration of symptoms was observed in 54 patients due to the primary conservative care, so they needed no surgical treatment. The initial assessment of the severity of acute pancreatitis was based on local symptoms and laboratory indices; the clinical diagnostics of pancreonecrosis was taken into account. At the second stage, the severity of the disease was assessed based on the physiological condition of patients and several clinical and laboratory criteria. The Ranson (1974), Imri (1984) and APACHE II (1984) scores were used as the most common clinical and laboratory integral scales.

The Sepsis-related (Sequential) Organ Failure Assessment (SOFA) score was used to assess the signs of polyorganic insufficiency. The use of the SOFA score enables standardizing the clinical trials, tracing the POI dynamics and comparing the therapeutic results in different groups of patients.

The following parameters were used to assess the hemostatic system: platelet count, ADP-induced platelet aggregation, R+K indices based on thromboelastography data, activated partial thromboplastin time (APTT), prothrombin index (PTI); levels of antithrombin III (AT-III), fibrinopeptide A (FpA), D-dimer and fibrin/fibrinogen degradation products (FDP); as well as the blood levels of pancreatic enzymes, hepatic tests (ALT, AST, alkaline phosphatase, bilirubin, bilirubin fractions), C-reactive protein and fibrinolytic activity of blood (FAB).

RESULTS

In addition to the specific clinical symptoms that are typical of patients with acute pancreatitis, the examined patients exhibited intoxication and water–electrolyte imbalance. The treatment started with infusion therapy, correction of acute volemiya and of the water and electrolyte balance.

The hypercoagulation syndrome was observed in patients with destructive pancreatitis during the pre-surgical period; the manifestations of the syndrome included an increase in the platelet aggregation activity, a decrease in chronometric indices (R + K, APTT), an increase in the activation levels of fibrinogen, SFMC and fibrinogen degradation products (FDP), as well as activation of the hemostatic system.

It is important to note, that during a acute destructive pancreatitis of activation of system of a hemostasis it is observed since the first day.

An increase in platelet activation was observed in all patients (Table 1) 76.7±7.8% (N = 65.4±6.9%, p <0.05); however, the total platelet count was within the normal range. A decrease in time to R + K 30.2±3.4 mm (n=37.3±3.6 mm, p<0.05) and 31.7±3.1 APTT (n=34.3±3.6, p<0.05) was observed for the chronometric indices.

The prothrombin index deviated from the normal range. Fibrinogen density was elevated to 3.6 ± 0.4 g/l (n=2.8±0.3 g/l; p<0.05). Fibrinogen is known to be an acute-phase protein; an increase in its level indicates the presence of the inflammatory process in patients. Furthermore, an elevation of the level of soluble fibrin monomer complexes to 0.52±0.05 units was observed (the normal level being 0.42±0.04 units, p<0.05). It was established that fibrin complexes with fibrin monomer and high-molecular-weight degradation products emerge after the cleavage of fibrinopeptides A and B from fibrin and under the influence of thrombin. Thus, an elevated blood concentration of SFMC attests to an increase in the rate of thrombin formation. An increase in the FpA index to 2.2±0.4 ng/ml (n=1.8±0.3 ng/ml, p<0.05) is the reliable evidence of the increase in the level of thrombocytopenia. The rapid and short-term elimination of circulating FpA is a reliable criterion showing its actual concentration in patient’s blood and, therefore, the activation of the hemostatic system.

Moreover, an increase in the FDP level to 8.4±2.1 µg/ml (n=4.7±1.8 µg/ml, p<0.05) associated with the changes in FAB was observed. At this stage of studies, blood concentration of D-dimer was within the normal range. The AT-III level was also within the normal range. Thus, activation of the hemostatic system manifesting itself as the hypercoagulation syndrome was observed in patients with acute destructive pancreatitis at the early stage of the disease development already in the pre-surgical period.

A traumatic injury caused by surgical intervention and general anesthesia carried out upon acute destructive pancreatitis negatively affect the hemostatic system. The key factors causing the changes in the blood coagulation system upon surgical intervention and anesthesia include surgical stress (tissue damage, hemorrhage), effects of the administered anesthetic

Table 1: Comparative characterization of the hemostatic system indices upon acute destructive pancreatitis with the normal indices. n=125

N ^o	Indices	Normal	In ADP patients
1	Platelet count per 1 µl	275245±26321	276527±24383
2	ADP-induced platelet aggregation, %	65.4±6.9	76.7±7.8*
3	R+K, mm	37.3±3.6	30.2±3.4*
4	APTT, s	34.3±3.5	31.7±3.1*
5	Fibrinogen, g/l	2.8±0.3	3.6±0.4*
6	PTI, %	96.8±7.4	94.7±8.7
7	SFMC, extinction units	0.42±0.04	0.52±0.05*
8	FpA, ng/ml	1.8±0.3	2.2±0.4*
9	FDP, µg/ml	4.7±1.8	8.4±2.1*
10	D-dimer, ng/ml	233.3±64.5	240.7±69.1
11	AT-III,%	98.3±9.7	97.8±9.4
12	FAB,%	44.9±5.2	45.6±4.9

*- p<0.05 compared to the normal values.

Table 2: Characteristics of the hemostatic system in surgical and nonsurgical patients

N ^o	Indices	Surgical patients n=54			Nonsurgical patients. n=71		
		Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
1	Platelet count per 1 µl	242347±25079*	217349±22836*	213106±21941*	240432±23074	201576±24172	210730±22972
2	ADP-induced platelet aggregation, %	73.5±8.3*	56.6±6.8*	61.7±7.1	74.6±7.8	55.7±6.8	62.3±7.4
3	R+K, mm	32.6±3.6*	31.7±3.3*	36.73±3.9	31.7±3.7	30.4±3.5	36.5±4.0
4	APTT, s	30.9±3.2*	29.9±3.1*	34.4±3.1	30.2±3.3	29.1±3.2	33.2±3.3
5	Fibrinogen, g/l	3.8±0.5*	5.5±0.6*	5.1±0.5*	3.8±0.4	5.6±0.6	5.2±0.5
6	PTI, %	94.8±8.7*	88.3±8.2*	90.8±8.3*	93.6±8.5	85.1±8.1	86.2±8.2
7	SFMC, extinction units	0.72±0.0*	1.01±0.1*	0.94±0.1*	0.74±0.08	1.12±0.14	1.07±0.12
8	FpA, ng/ml	3.7±0.4*	7.5±0.7*	5.8±0.5*	3.8±0.4	8.7±0.5	6.4±0.5
9	FDP, µg/ml	12.3±2.0*	40.1±6.0*	41.8±5.9*	12.7±2.3	46.3±7.7	44.3±6.5
10	D-dimer, ng/ml	512.7±109.4*	756.1±117.3*	622.5±100.4*	787.5±111.7	985.2±122.3	823.9±119.1
11	ÀÖ-III, %	93.7±9.2	88.4±8.9*	86.4±9.1*	94.2±9.3	82.4±9.1	85.1±9.2
12	FAB, %	42.1±4.6	40.1±4.3*	41.9±4.8	42.7±5.4	39.7±4.4	41.7±4.9

* – p<0.05 compared to the normal values.

** – p<0.05 compared to the patients who underwent surgical treatment.

agents and drugs. The effect of these factors on the hemocoagulation system was purposefully not taken into account; thus, this question has elucidated the course of the study. The aim of our study was to investigate the hemostatic system in patients with acute destructive pancreatitis during the pre-surgical and surgical periods.

It is important to note that the dynamics and prognosis of the disease in patients with severe disseminated purulent peritonitis and destructive pancreatitis is determined not only by surgical intervention, but also is to a significant degree determined by complications (in particular, manifestations of polyorganic insufficiency). This fact was attested by clinical and laboratory studies performed in patients with severe condition. The patients were subsequently retrospectively divided into two subgroups: nonsurgical ones and patients who underwent pancreatic surgery. The data relating to the subgroups are listed in Table 2.

When analyzing the hemostatic system indices in patients who underwent surgery and those who received conservative therapy without surgical intervention, one should note the differences in the D-dimer level on day 1 in surgical patients. The D-dimer level was equal to 1061.2±112.8 ng/ml and 512.7±109.4 ng/ml (p<0.05) in surgical and nonsurgical patients, respectively. These indices were higher than the normal ones in both subgroups. No differences in the other indices have been observed for the subgroups. Moreover, a decrease in AT-III activity in nonsurgical patients was observed. The results showing lower levels of C-reactive protein and AT-III, as well as fibrinolysis suppression in surgical patients compared to those in nonsurgical ones, coincide with the literature data.

We have performed clinical laboratory comparison to establish that the maximum level of POI corresponds to the peak activation of the hemocoagulation system and suppression of the coagulation systems. The degree of POI intensity was assessed using the SOFA score. A positive correlation between the severity of POI and concentrations of FpA and D-dimer was detected in patients on days 1–5 after the surgery; the correlation coefficients were 0.69 and 0.72, respectively. This fact indicates that the intravascular blood coagulation contributes to the formation of POI.

At a acute destructive pancreatitis in parallel with studying parameters of system of a hemostasis at all patients after operation carried out an estimation of weight on scale APACHE II, all physiological parameters spent in view of a complex, age and accompanying diseases.

The prognostic value of the APACHE II scale was proved in clinical studies. In our study, the severity of condition of the patients on day 1 after hospitalization was assessed using the APACHE II scoring system; a direct correlation between the severity of patients' condition and the lethal outcome was detected.

In our study, the severity of condition based on the APACHE II scoring system in group 1 patients on day 1 after admission to the intensive care unit was 16.2±3.2. The further retrospective analysis has shown that the severity of condition was 12.1±2.7 and 19.9±2.8 in the patients who have survived and died, respectively (p<0.05).

The correlation between the hemostatic indices under study and the APACHE II severity of condition in patients on day 1 after the surgery was also investigated.

A direct correlation between plasma concentration of D-dimer and the severity of condition was revealed ($q = 0.71$).

An increase in D-dimer level to 2000 ng/ml was observed in patients with the diagnosed DIC syndrome; a decrease in antithrombin III level and an elevation in concentrations of FpA and FDP were simultaneously detected. This is associated with the activation of the blood coagulation system, consumption of the main anticoagulants and lysis of intravascular fibrin deposits due to secondary fibrinolysis. It has been established in some studies that in a number of cases (benign and malignant tumors of the prostate gland), the level of D-dimer remained within the normal range upon primary fibrinogenolysis; however, it was fibrinogen (not fibrin) that participated in this process. With allowance for theoretical reasons, in addition to the other indices (FpA, fragments of prothrombin 1 +2 with thromboglobulin 3, with thrombin-antithrombin-III complex), a rapid increase in the D-dimer level in patients with the DIC syndrome gives grounds to regard the D-dimer as a marker of activation of the blood coagulation system and fibrinolysis. In fact in plasma D-dimers it is important for occurrence not only activation of curtailing of blood and adjournment of fibrin on an internal surface of blood vessels, but also age features for fibrinolytic activity of blood (or at least clear processes of braking).

It would be more reasonable to assume that the D-dimer level can remain within the normal range upon inhibition of fibrinolysis even upon the emergence of thrombi in great vessels and thromboembolia. On the contrary, an abrupt increase in D-dimer level was observed for different thrombus localization under pressure of therapy with various thrombolytic agents. It was refined by analyzing the resulting data that the D-dimer level in patients with acute destructive pancreatitis in severe condition on day 1 after the surgical intervention varies depending on the disease course; a direct correlation between the condition of the patients and the plasma level of D-dimer is observed. Therefore, an increase in plasma level of D-dimer is an unfavorable prognostic factor. Nevertheless, neither relationship between the other hemostatic factors nor one between the FDP level and the severity of patient condition has been revealed at this level of studies.

An increase in D-dimer concentration in patients with acute destructive pancreatitis evaluated on day 1 after disease onset shows the formation and lysis of fibrin.

The failure of endogeneous anticoagulant factors to prevent fibrin formation is a negative prognostic factor. Fibrin deposition on capillary walls as a result of disseminated intravascular coagulation disrupts the supply of blood and oxygen to organs and tissues, simultaneously impeding metabolite elimination. It is a significant factor of development of polyorganic insufficiency in patients with disseminated purulent peritonitis and acute destructive pancreatitis. The comparison of the clinical and laboratory indices suggested that the peak of activation of the hemostatic system and suppression of the anticoagulant system corresponds to the maximum severity of POI.

The degree of manifestation of POI was assessed using the SOFA score. The total SOFA score was calculated every day and was used at a certain instant to determine the severity of organ failure. Determination of the degree of severity of POI based on the SOFA score is the key index; it is valid to say that this fact refers to the entire department of surgical reanimation. The efficiency of the SOFA score has been confirmed in clinical practice. In order to determine the role of hemocoagulation disorder in the development and course of complications, the relationship between the major indices under study and the degree of severity of POI was ascertained.

DISCUSSIONS

A positive correlation between the degree of severity of POI and concentrations of FpA and D-dimer was revealed on days 1-5 of the post-surgical period; the correlation coefficients were 0.69 and 0.72, respectively. This attests to the fact that intravascular coagulation contributes to the development of POI. Meanwhile, no relationship between the other parameters and the severity of POI has been revealed. It is on days 3-5 that a significant decrease in the AT-III level is observed.

In our studies, the development of POI in patients with destructive pancreatitis typically begins with the emergence of respiratory failure. Renal and hepatic dysfunctions along with the other syndromes subsequently develop. It should be noted that the emergence of respiratory failure deteriorates disease prognosis and course [5, 15].

Based on the resulting data, one can conclude that activation of the hemostatic system in surgical patients with acute destructive pancreatitis is the key component in the development of early and late

complications. The D-dimer level showing fibrin formation and lysis estimated on day 1 after the disease onset correlates with the severity of patient condition [3, 5, 13]. Excessive activation of the hemostatic system determined based on the plasma level of D-dimer is a negative prognostic factor. The disorder of the hemostatic system subsequently gets worse; the AT-III level (the major component of antithrombin activity of the organism) decreases. All these facts attest to a severe imbalance of the hemocoagulation system accompanied by a failure of the compensatory potential. A direct correlation between the plasma level of D-dimer and the severity of patient condition was revealed when comparing these factors. Progression of POI and deterioration of the patients' condition was also observed. A positive correlation between the degree of severity of POI and concentrations of FpA and D-dimer was observed in the dynamics of the acute period [11, 13, 15].

Thus, the development of POI is accompanied by the formation of a combination of complex metabolic disorders, which cannot be eliminated by using only the infusion and antibacterial therapy. The analysis of the resulting data attests to the fact that intravascular blood coagulation contributes to the emergence and development of POI [10, 13, 15]. It is important to note that these data were obtained during the anticoagulant therapy. Our studies set conditions for further investigation of the methods for correction of the revealed disorders and the mechanisms of changes in the hemostatic system in patients with acute destructive pancreatitis. Therefore, the plasma levels of FpA and D-dimer in patients with acute destructive pancreatitis are the key indices of activation of the human hemostatic system, which enables early diagnosis and makes it possible to control this disease and, in particular, pancreatic necrosis.

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