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Hemocoagulation factors of hemorrhagic complications in acute pancreatitis

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A feature of the severe condition of acute pancreatitis is the high risk of complications occurring in 50% of patients. The most dangerous are thrombohemorrhagic complications and arrosive bleeding, with late diagnosis of which mortality can reach more than 85%. The aim of the study was to determine early diagnostic criteria for the onset and development of bleeding in acute pancreatitis. The results of treatment of 82 patients with severe acute pancreatitis were analyzed. The patients were divided into the main group (with bleeding) (30 people) and the comparison group (without bleeding) (52 people). The parameters of hemocoagulation, α-amylase activity in peritoneal exudate and intra-abdominal pressure were assessed. The tPA activity and the level of TAT in the main group were of normative value and are vital for the group of individuals who are in the range of norms, as well as candidates for early markers for the diagnosis of bleeding. From the ROC analysis, the analysis determined the informativeness of the proposed indicators in the predicted bleeding. For tPA activity, the area under the ROC-curve (AUROC) became 0.942 (95% CI 0.889-0.995), the point of change is 4,5 IU/ml, for the TAT area under the ROC-curve (AUROC) it became 0.945 (95% DI 0.871-0.998), the change point is 11.5 ng/ml. We conclude that in patients with severe acute pancreatitis, a tPA activity level ≥4.5 IU/ml (sensitivity 90.2%, specificity 83.3%) and/or a TAT level ≥ 11.5 ng/ml (sensitivity 92.2%, specificity 83.3%) can be considered as a possible predictor of bleeding.
Key words: acute pancreatitis; arrosive bleeding; coagulation disorders.

INTRODUCTION

Acute pancreatitis accounts for about 25% of cases in the structure of acute abdominal surgical pathology and is one of the most pressing problems of modern medicine [1]. The peculiarity of the disease is the high risk of complications observed in 50% of patients with the average mortality level of 5.5% and reaching 40-70% in cases of severe pancreatitis [2]. It should be noted that currently many clinical prognostic markers of severe acute pancreatitis (old age, obesity, high hematocrit and C-reactive protein) have been proposed [3, 4]. Other prognostic markers of severe acute pancreatitis include elevated levels of interleukin-6 (IL-6), interleukin-10 (IL-10), procalcitonin, and tissue plasminogen activator (PLAT) [5]. For prediction the onset of multiorgan failure syndrome, the determination of the combination of plasma concentrations of IL-10 and calcium is used [6]. Although purulent-septic complications often develop in severe cases of acute pancreatitis, the most dangerous are thrombohemorrhagic complications and arrosive bleeding, in the late diagnosis of which mortality can reach more than 85% [7].

According to the literature, the causes of thrombohemorrhagic complications in destructive acute pancreatitis are changes in the rheological properties of blood, microcirculation in the area of tissue destruction and beyond, changes in blood coagulation potential until the development of Disseminated intravascular coagulation (DIC) syndrome, a sharp increase in permeability of microvascular walls under the influence of pancreatic aggression [8]. Activation of the fibrinolytic system of blood with emergence of widespread hemorrhages against fabric hypostasis is observed. Subsequently, with a

decrease in the proteolytic activity of blood, the process of thrombosis begins in the vessels of the damaged pancreas, the surrounding tissue, as well as in other vascular regions (manifestations of systemic thrombophilia) with the occurrence of abdominal infarctions. On the other hand, there is a pronounced coagulopathy in acute pancreatitis, mainly due to a decrease in total platelet count and fibrinogen concentration in blood plasma, especially as a result of activation of fibrinolysis [9].

The causes of erosive bleeding may be the result of ruptures of the mucous membrane in the cardioesophageal junction (Mallory-Weiss syndrome), acute erosions and ulcers of the digestive tract, as well as arising from vessels feeding the pancreas, usually in the purulent phase, sequestration and melting of necrotized parenchyma of the organ and parapancreatic tissue. Sources of arrosive bleeding are usually large arteries and venous trunks. Also, there is the development of arrosive bleeding in the postoperative period in 3.5-8.5% of patients with acute pancreatitis [10]. Currently, the diagnosis of thrombohemorrhagic complications is based on clinical and laboratory signs that appear after the onset of bleeding, which significantly limits the possibilities of conservative therapy and worsens the prognosis, while early diagnostic markers are not identified.

The aim of this work is to determine the early diagnostic criteria for occurrence and development of bleeding in acute pancreatitis.

METHODS

In the period from 2017 to 2020 we analyzed the results of examination and treatment of 82 patients with acute pancreatitis, who were hospitalized in the clinic of the Department of Surgery No. 2 Bogomolets National Medical University.

Among the surveyed were 59 (71.9%) men and 23 (28.1%) women, 18.3% of young people (under 44 years), 64.6% - middle-aged (from 44 to 60 years) and 17.1% of the elderly (over 60 years) patients. The study included patients with severe disease according to the International Association of Pancreatology Classification (Kochin, India, 2011) and Acute Pancreatitis Classification Working Group (2012). According to etiological factors, acute pancreatitis of biliary etiology occurred in 13 (15.6%) patients, alcoholic - in 69 (84.1%) patients. 61 (74.4%) patients were operated, 21 (25.6%) patients were treated conservatively. Indications for surgery in the early phase of the disease were acute pancreatitis of biliary etiology, namely 10 (12.2%) patients underwent endoscopic surgery to internal decompression of the duct system and restore the passage of bile and pancreatic juice into the duodenum. Thus, 6 (7.3%) patients underwent endoscopic papillosphincterotomy (EPST) with revision of the duct system and extraction of stones, indications of which were the phenomena of scar stenotic papillitis, cholangitis and choledocholithiasis. Two (2.4%) patients with functional muscle spasm and the absence of gross scarring of the walls of the biliary tract were underwent mechanical (balloon) dilation and the other two (2.4%) patients - pharmacological (myogenic antispasmodics) dilatation of the distal ducts and large duodenal papilla.

Laparotomy within 2 weeks from the onset of acute pancreatitis was performed in 12 (14.6%) patients with widespread purulent peritonitis with the development of multiple organ failure. In the late phase of acute pancreatitis indications for surgery were infection of necrosis with the formation of abscesses (sequesters) of the pancreas and the occurrence of phlegmon of the retroperitoneal tissue. Thus, 9 (10.9%) patients underwent laparotomy, necrosequrectomy, abdominal abdominology, drainage of the abdominal cavity and retroperitoneal space, 4 (4.9%) patients underwent laparoscopic opening of the omental sac, necrosequrectomy, drainage of the abdominal cavity. It should be noted that when choosing the type of surgery, preference was given to minimally invasive interventions and puncture echo-controlled treatments with different approaches, which were performed in

26 (31.7%) patients. In the case of ineffective drainage under ultrasound control and disease progression (including the development of arosive bleeding) in 3 (3.7%) patients underwent retroperitoneoscopic assisted necrosequrectomy, in 3 (3.7%) patients - combined laparoscopic and retroperitoneal necresequrectomy and in 4 (4.9%) patients - open laparotomy, necrosequrectomy, drainage of the abdominal cavity and retroperitoneal space.

Occurrence of thrombohemorrhagic complications in severe acute pancreatitis was observed in 30 (36.6%) patients, they were included in the main group, the comparison group consisted of 52 patients.

The following parameters of the coagulation system were determined in all patients: plasma fibrinogen content, international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT), activity of tissue plasminogen activator (PLAT), activator inhibitor type-1 (PAI-1) and the level of excessive thrombin-antithrombin III complex (TAT). Patients were also tested for intra-abdominal pressure (IAP) and the activity of pancreatic enzymes (α-amylase) in the contents of the abdominal cavity in the case of surgery.

The evaluation of the results was performed on the day of bleeding in patients of the main group, and on the 14th day after the disease in patients of the comparison group (corresponding to the average day of bleeding in the main group).

Statistical analysis was performed using the program SSPS 22, the normality of the data distribution was determined by the Shapiro-Wilk test. In the case of nonparametric distribution of the analyzed data, the results were presented as averages and their standard deviation (M ± SD), in nonparametric - as the median and quartile (Me [Q25-Q75]). The difference between the groups was established using Student's t test for independent samples by parametric and Mann-Whitney by nonparametric distribution. Cutting points and their informativeness were determined using ROC analysis. Differences between indicators were considered significant at $P < 0.05$.

RESULTS

Source of bleeding of patients of the main group were: erosive gastritis in 10 (30%) cases (of which 7 (23.3%) patients were treated with conservative drugs), Mallory-Weiss syndrome - 2 (6.7%) patients (conservative therapy was used to treat acute pancreatitis in both cases), acute duodenal ulcer - 4 (13.3%) patients (of which two (6.7%) patients used conservative drugs), bleeding from the vessels of the pancreas after laparotomy, necrosequectomy, drainage of the abdominal cavity and retroperitoneal space - 6 (20%) patients, bleeding from the vessels of the pancreas after laparoscopic opening of the omental sac, necrosequrectomy, drainage of the abdominal cavity - two (6.7%) patients, puncture methods of treatment were controlled by ultrasound - 4 (13.3%) patients, after performing EPST - two (6.7%) patients.

When determining the time of bleeding from the moment of the disease in patients who received only conservative therapy of acute pancreatitis, the latter occurred at 6.1 ± 2.9 days, in patients who also underwent surgical treatment - at 17.7 ± 11.3 days, respectively. In general, bleeding occurred at 13.8 ± 10.8 days in the main group. Conservative measures were used in 19 (63.3%) cases and surgical treatment in 11 (36.7%) cases to stop bleeding in patients of the main group. Conservative treatment was performed according to existing protocols, surgical treatment - two (6.7%) patients were performed fibrogastroduodenoscopy (FGDS), electrocoagulation of the duodenal mucosa (after EPST); 3 (10%) patients - FGDS, spraying of adhesive and film-forming substances (caprofer) on the surface of acute duodenal ulcer; and 6 (20%) cases - relaparotomy, hemostasis, tamponade of the bleeding place, lavage, drainage of the abdominal cavity.

Patients with thrombohemorrhagic complications and the comparison groups did not differ significantly in age (50 ± 9.1 and 52.7 ± 9.9

years, P > 0.05, respectively) and gender (men 73.3% and 71.2%, women 26.7% and 28.8%, P > 0.05, respectively). There were also no differences in the analysis of the etiology of the disease. Thus, in the main group, patients with pancreatitis of biliary etiology composed 10% and of alcoholic - 90%. In the comparison group, the respected values amounted 19.2% and 80.8%, P > 0.05, respectively). The severity of the disease according to the scale APACHE II amounted 15.9 ± 7.9 points in the main group and 14.9 ± 7.1 in the comparison group, P > 0.05, respectively. No differences in treatment tactics were found. Among patients with bleeding, 20 (66.7%) were underwent surgical treatment, 10 (33.3%) patients were prescribed conservative therapy. In the comparison group - 11 (21.2%) patients were treated conservatively, surgical treatment was used in 41 (78.8%) patients (P > 0.05, respectively).

Due to the lack of other predictors, the analysis of coagulogram parameters was performed to determine early markers of bleeding in severe acute pancreatitis (Table).

Fibrinogen levels were likely to be higher in patients with bleeding, but remained within normal limits in both groups and therefore could not be used to predict bleeding. On the other hand, INR, PT and aPTT were above the upper limit of the norm in both groups, although in patients with bleeding they were probably higher, they also cannot be predictors. PAI-1 activity was probably lower in the main group, but remained within normal limits, so it also cannot be used to predict bleeding.

PLAT activity and the TAT level in the main group were higher than the normative values and probably higher than in the comparison group, in which it remained within the norm, and, therefore, are candidates for early markers of bleeding. The informativeness of the proposed indicators in the prediction of bleeding was determined using ROC analysis. For PLAT, the area under the ROC-curve (AUROC) is 0.942 (95% CI 0.889–0.995; P = 0.001), the cut-off point corresponds to 4.5 IU/ml. For TAT, the area under the ROC-curve (AUROC) is 0.945 (95% CI 0.871–0.998; P = 0.001), the cut-off point corresponds to 11.5 ng/ml. That is, for patients with severe acute pancreatitis, the level of PLAT ≥4.5 IU/ml (sensitivity 90.2%, specificity 83.3%) and / or the level of TAT ≥11.5 ng/ml (sensitivity 92.2%, specificity 83,3%) can be considered as a probable predictor of bleeding.

There was no statistically significant difference between the values of IAP and the level of α-amylase activity in the contents of the abdominal cavity, and IAP was increased in both groups, but in patients of the main group this indicator was higher (16.5 ± 3.6 mm Hg against 12.1 ± 1.9 mm Hg) (P > 0.05). The level of α-amylase activity in the contents of the abdominal cavity was also increased in both groups and was in patients of the main group 771.7 ± 188.7 U/l and the comparison group - 311.2 ± 288.4 U/l (P > 0.05).

Indicators of coagulogram in patients with severe acute pancreatitis

Tests	Rate	Main group (n = 30)	Comparison group (n = 52)	P
Fibrinogen, g/l	2.0-4.0	2.6 [2.2-2.8]	3.9 [3.6-4.0]	<0.0001
INR	0.8-1.2	3.3 [2.5-3.5]	2.6 [2.0-3.0]	<0.0001
PT, s	9.2-12.2	26.3 [24.2-30.2]	19.0 [14.0-22.0]	<0.0001
aPTT, s	25.4-38.4	57.3 [48.4-62.2]	43.0 [38.0-47.0]	<0.0001
PLAT activity, IU/ml	1.75-2.4	5.9 [5.4-6.2]	0.4 [0.2-0.5]	<0.0001
PAI-1 activity, IU/ml	0.4-15	0.3 [0.2-0.4]	40.0 [35.0-46.0]	<0.0001
TAT level, ng/ml	3.7-8.5	13.0 [12.0-14.0]	0 [0-1.0]	<0.0001

Note: INR (international normalized ratio), PT (prothrombin time), aPTT (activated partial thromboplastin time), PLAT (activity of tissue plasminogen activator), PAI-1a (ctivator inhibitor type-1), TAT level (the level of excessive thrombin-antithrombin III complex), data are given in the form of Me [Q25-Q75].

DISCUSSION

The data regarding indicators of blood coagulation system necessitate their constant monitoring for the purpose of early detection of preconditions of occurrence of bleeding in patients with severe course of acute pancreatitis and their prevention. The incidence of bleeding in patients of this category, according to our study, can reach 36.6%, and the time of onset is 13.8 ± 10.8 days, which corresponds to both early and late periods of the disease. The main source of bleeding were erosive-ulcerative lesions of the gastrointestinal tract (16 (19.5%) patients), the development of which is explained by the stressful effects of the destructive process in the pancreas and concomitant severe endogenous intoxication. In 14 (17.1%) patients, erosive bleeding occurred in the postoperative period, which, in our opinion, was due primarily to the secretion of pancreas, rich in proteo- and lipolytic enzymes, under the influence of which erosion may occur (destruction, ulceration, necrosis) of the vascular wall with the development of bleeding.

By analyzing the process of hemocoagulation in patients with severe acute pancreatitis, it can be argued that the disease develops as a type of consumption coagulopathy with activation and subsequent depletion of components of the coagulation system, secondary activation of fibrinolysis, and, consequently, leads to multiorgan failure syndrome and bleeding. Therefore, during the treatment of patients with acute pancreatitis it should be taken into account the possibility of thrombohemorrhagic complications, early diagnosis of which will improve treatment outcomes and solve the problem of prevention of erosive bleeding from the pancreas in the postoperative period. Among the indicators of the coagulogram, the greatest sensitivity in the prognosis of bleeding in severe acute pancreatitis were PLAT activity and TAT. The PLAT activity values ≥4.5 IU/ml (sensitivity 90.2%, specificity 83.3%) and/or TAT level ≥11, 5 ng/ml (sensitivity 92.2%, specificity 83.3%) can be considered as a probable predictor of thrombohemorrhagic complications in severe disease.

Thus, abnormalities in coagulation hemostasis and the activity of pancreatic enzymes in the contents of the abdominal cavity are the leading etiological factors of erosive bleeding from the body in acute pancreatitis. Determination of TAT and PLAT can be used to screen for bleeding in severe acute pancreatitis.

CONCLUSIONS

1. Severe acute pancreatitis is characterized by hemocoagulation disorders and can be complicated by the development of bleeding in 36.6% of cases.

2. The main source of bleeding in severe acute pancreatitis are erosive-ulcerative lesions of the gastrointestinal tract (19.5% of patients), the development of which can be explained by the stress of the destructive process in the pancreas and concomitant severe endogenous intoxication.

3. In 17.1% of patients, bleeding occurred in the postoperative period and was associated with the erosive action of pancreatic secretions.

4. In patients with severe acute pancreatitis, the level of PLAT activity ≥4.5 IU/ml (sensitivity 90.2%, specificity 83.3%) and / or the level of TAT ≥11.5 ng/ml (sensitivity 92.2%, specificity 83.3%) can be considered as a probable predictor of bleeding.

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ГЕМОКОАГУЛЯЦІЙНІ ЧИННИКИ ВИНИКНЕННЯ ГЕМОРАГІЧНИХ УСКЛАДНЕНЬ ПРИ ГОСТРОМУ ПАНКРЕАТИТІ

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Визначали ранні діагностичні критерії виникнення та розвитку кровотеч у хворих з тяжким перебігом гострого панкреатиту. Для порівняння отриманих результатів пацієнти були розподілені на основну групу (30 хворих у яких розвинулись кровотечі) та групу порівняння (52 пацієнта). Оцінювали показники гемокоагуляції, активності α-амілази в перитонеальному ексудаті та внутрішньочеревний тиск. Активність тканинного активатора плазміногену (ТАП) та вміст тромбін-антитромбін ІІІ-комплексу (ТАТ) в основній групі були вищими нормативних значень та вірогідно вищим, ніж у осіб групи порівняння, в яких він залишався в межах норми, а отже є ранніми маркерами виникнення кровотечі. Із застосування ROC-аналізу визначено інформативність запропонованих показників у прогнозуванні кровотеч. Для ТАП площа під ROC-кривою (AUROC) становила 0,942 (95% ДІ 0,889–0,995), відрізна точка відповідає 4,5 МО/мл, для ТАТ площа під ROC-кривою (AUROC) становила 0,945 (95% ДІ 0,871–0,998), відрізна точка відповідає 11,5 нг/мл. Таким чином, у пацієнтів з тяжким перебігом гострого панкреатиту активність ТАП ≥4,5 МО/мл (чутливість 90,2%, специфічність 83,3%) та/або вміст ТАТ ≥11,5 нг/мл (чутливість 92,2%, специфічність 83,3%) можна розглядати як вірогідний предиктор виникнення кровотечі.

Ключові слова: гострий панкреатит; арозивна кровотеча; порушення коагуляції.

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