UDC

TARABRIN O.A., SCHERBAKOV S.S.
Odessa National Medical University

SPECIFIC FEATURES OF DIAGNOSIS OF HEMOSTATIC DISORDERS AND OPTIMIZATION OF INFUSION THERAPY IN SEVERE COURSE OF DESTRUCTIVE PANCREATITIS

Abstract. *The paper pathogenetically substantiates and approves methods to improve the efficacy of treating destructive pancreatitis with the use of express diagnosis, and to correct hemostatic disorders, and also analyzes clinical experience of using Gecoton, a multi-component, polyionic, colloid hyperosmolar solution of a new generation, in the complex treatment of pancreatic shock. The study was conducted in 86 patients with severe forms of acute destructive pancreatitis. The hemostatic system was evaluated using indicators of analyzer ARP-01 "Mednord" (low-frequency piezoelectric thromboelastography, LPTEG), by means of classical laboratory tests. The use of thrombelastography method enabled hemostatic disorders in acute period of destructive pancreatitis to be timely evaluated with minimal material costs and within a short time, directly at the bedside. Specific correction of hemostatic disorders in destructive pancreatitis via impacting on the key pathogenetic factors through Gecoton, purpose-oriented prescription of LPTEG with different mechanisms of action — Latren, trasylol, fresh-frozen plasma — and therapeutic plasmapheresis makes it possible to decrease the incidence of pulmonary complications by 1.7 times, reduces the duration of stay at in-patient facility by 23 %, as well as diminishes lethality in severe course of disease by 30.9%.*

In acute pancreatitis morbidity patterns, there is seen a growth in the number of its destructive forms, where the lethality, according to different authors, varies from 8 to 70% due to the development of severe endogenic intoxication and formation of multi-organ failure [1, 12]. In acute pancreatitis pathogenesis, a significant place is taken by the hemostatic system disorders, which are manifested in the development of thromboses and/or hemorrhages. The complexity of pathology explains the existence of different, at times antagonistic views on the hemostatic system condition in early forms of acute destructive pancreatitis (ADP) [3, 6]. The issues of prognosticating ADP course and outcomes, choice of therapeutic methods and regimens, monitoring of destructive processes in the grand still remain debatable.

In this context, it is no wonder that alongside with the issues of diagnosis and surgical tactics the problem of intensive therapy continues to be actively discussed. To eliminate volemic abnormalities is one of the tasks in the basic intensive therapy of ADP patients. Most adequately it is solved in the course of intensive therapy with the use of volemically active plasma substitutes. Within the last decade, in many countries of the world, the class of drugs based on hydroxyethylated starch occupied the leading position among colloid volume-substitutive solutions, having sidelined plasma-substitutive agents based on dextran and gelatin [2, 7].

Steady growth of acute pancreatitis morbidity, especially its destruc-tive forms, high lethality level and numerous complications, not infrequently leading to severe impairments of bodily functions up to incapacitation, as well as the existing diagnosis complexities and lack of a single approach to the treatment of this disease, enforce to pay attention to studying this pathology.

Objective of the study — to pathogenically substantiate and approve the methods of enhancing the efficacy of destructive pancreatitis treatment with the aid of express-diagnosis, and to correct hemostatic disorders, as well as to analyze clinical experience of using multi-component polyionic colloid hyperosmolar, new generation solution Gecoton, for the comprehensive treatment of pancreatic shock.

Materials and methods

The study was carried out in 86 patients with severe forms of ADP, who were divided in 2 groups: 1st group (n = 32) — patients with traditional management of pancreatitis; 2nd group (n = 54) — patients who were additionally given specific correction of the revealed coagulative disorders. The data obtained were compared with those from the control group — 25 practically healthy persons (donors). Distribution of patients in the 1st and 2nd groups by age, sex, disease severity and acute pancreatitis complications was rather comparable. In all cases, the availability of pancreatic shock was established on the basis of clinical and instrumental examination methods. An average number of points according to SAPS II score in the 1st group amounted to 33.6 ± 9.2, in the 2nd group — 34.1 ± 8.4. In 1-2 days, patients underwent laparotomy of a sanative character. Hemostatic system condition was evaluated, using readings of analyzer ARP-01 "Mednord" (low-frequency piezoelectric thromboelastography — LPTEG), which, according to the literature data, gives a possibility to evaluate the condition of the whole hemostatic system, rather than the level of its individual parameters. Preliminarily, the above hemostatic indicators were found to correlate with those determined by classical laboratory tests. The efficacy of intensive therapy was evaluated by the dynamics of hemostatic system indicators, amylolytic activity of the blood and abdominal cavity exudate on the 1st, 3rd, 5th and 7th days since the disease onset, character of complications, duration of treatment at the ICU department and bed day at the in-patient facility, lethality and its causes.

Results and discussion

Even in the first 24 hours, patients with destructive pancreatitis revealed essential shifts in the hemostatc system component links, and along with this, the shifts were of ambiguous character (Table 1).

Within the first 24 hours, an increase in the intensity of spontaneous platelet aggregation (An) is seen, while their retractile ability increases averagely by 15%. The time of a clot formation start (r) diminishes by 70%, and thrombin constant (k) — by 25%. The intensity of thrombin formation (Kk) increases by 73%. As a result, the clot maximum density (AM) rises by 14%. With that, the time to form the clot fibrin-thrombocytic structure (T) does not change considerably.

By the 3rd day, the thrombin constant (k) reduces by 30% on an average, and the clot density increases by 20%. Fibrinolytic activity (F) drops by 60%. Despite the existing hemoconcentration, according to the data of hematocrit investigation (Ht = 0.49 ± 0.05) and increased indicator An LPTEG, the number of platelets in the blood appeared to be somewhat decreased and amounted to 184.5 ± 29.3 • 109/l (P > 0.05). The increased aggregation activity of the latter was indicated by the increased indicator r LPTEG.

In 7 days since the disease onset, index r remains to be lesser by 10% on an average, than that in the control, thrombin constant and maximum clot density do not change largely. The intensity of thrombin formation and spontaneous platelet aggregation remains to be increased by 40 and 15%, respectively. Indicator of fibrrinolysis rose by 53% as compared to the first day, but remains to be below the control values by 35%. Indicators of coagulative hemostasis in patients with destructive pancreatitis reflected pronounced hypercoagulative shift, clearly manifested in the changes of all chronometric and structural parameters of LPTEG, though not all of them are statistically significant. Changes in the indicators of a coagulogram biochemical tests had multidirectional character: prothrombin time (PT) increased from 15.4 ± 0.3 to 16.2 ± 0.4 s (P < 0.05), thrombin time (TT) did not practically change, while indicator APTT dropped from 44.6 ± 0.8 s to 35.7 ± 1.2 s (P < 0.05). These changes evidenced not only of hypercoagulation, but also of the development of acute disseminated intravascular blood coagulation (DIBC) with the signs of consumption coagulopathy. Conspicuous is the pronounced fibrinolysis activation. Comparing with healthy persons, the values of F LPTEG has grown up. The increase in indicator of the blood fibrinolytic activity on coagulogram also took place, but it was statistically insignificant. And along with it, appropriate are positive results of the coagulogram ethanol gelation and protamine sulfate tests. Thus, in ADP, since the first day, disorders in the hemostatic system are developed to correspond with coagulative clinico-pathogenic variant of DIC-syndrome — fibrinolysis inhibition and pronounced blood coagulation activity, remaining to exist during 7 days and having phased course.

Changes in the system of hemostasis were found to increase with the increase in the severity of destructive pancreatitis course, and were most significant in pancreatic shock against the background of unstable hemodynamics. From our viewpoint, the instability of hemodynamics in that period was due to the condition of microcirculation, regulated by the volume of adequate infusion therapy. The blood hemorheology correlated with the degree of intoxication (LII). Despite the signs of hemoconcentration, initial LPTEG indicator appeared to be decreased more than by 40% as compared to that in healthy persons (P < 0.05). The number of platelets in patients of this group was 105.2 ± 23.4 • 109/l, this being 2.5 times fewer than in healthy people. Most noticeably reduced was indicator Ar LPTEG. Disaggregation activity was identified not in all patients. Hemostatic coagulative link was characterized by the pronounced hypercoagulative shift over all chronometric and structural indicators of LPTEG and coagulogram. As this takes place, indicators of coagulative link (r, k, Kk) after primary change (the first day since the disease onset) did not normalize significantly later on. Maximum clot density as compared to the 1st day grows by 15%, regardless of the increased fibrinolytic activity. Such substantial changes, with account of twofold decrease of the total fibrinogen (P < 0.001) and platelets concentration made it clear that there takes place severe acute DIC-syndrome with bright laboratory manifestations of consumption coagulopathy, i.e. fibrinolytic variant of DIC-syndrome [11]. Lethality among these patient accounts for 70%, on an average.

Extraordinary complexity, variety and heterogeneity of morphologic and functional hemostatic disorders do not allow for offering an ambiguous and clearly-cut pattern of the infusion-transfusion therapy for all patients. Patients from the 1st group received traditional infusion-transfusion therapy under commonly accepted patterns, including the use of colloid, crystalloid solutions and blood preparations (FFP, albumin), hemodynamic blood substitutes, vasoconstrictors, disaggregants and anticoagulants (heparin 5,000 U, 6 times a day). Its real content was determined by the clinico-laboratory situation in a concrete patient, in a given moment of time.

Table 1. Dynamics of hemostatic indicators in acute period of destructive pancreatitis (M ± m)

Indicator	Control	Group	1st day	3rd day	5th day	7th day
An (rel.unit)	82,1 ± 2,1	1 2	93,1 ± 2,0 96,4 ± 1,1	104,5 ± 3,5 115,0 ± 1,9	74,6 ± 1,3* 74,3 ± 0,8*	74,2 ± 1,1* 74,5 ± 0,8*
r (min)	4,4 ± 0,3	1 2	2,5 ± 0,3* 3,6 ± 0,1* , **	3,7 ± 0,5 5,4 ± 0,1	4,4 ± 0,4 5,8 ± 0,1**	4,0 ± 0,3 5,0 ± 0,2
k (min)	4,5 ± 0,3	1 2	3,5 ± 0,4* 3,6 ± 0,2*	3,2 ± 0,3* 4,1 ± 0,2**	3,5 ± 0,3 4,3 ± 0,1**	3,6 ± 0,1* 4,6 ± 0,1**
AM (rel.unit)	667,0 ± 17,1	1 2	759,0 ± 30,6* 557,0 ± 13,8* , **	794,0 ± 26,3* 717,0 ± 12,3**	753,0 ± 25,3* 675,0 ± 9,9**	721,0 ± 30,3 654,0 ± 10,1**
T (min)	49,7 ± 2,1	1 2	49,1 ± 3,8 43,8 ± 1,1	49,8 ± 3,6 45,6 ± 0,8	44,1 ± 3,3 46,6 ± 0,7	49,4 ± 3,3 46,5 ± 0,5
F (%)	14,1 ± 2,9	1 2	5,7 ± 1,2* 6,7 ± 0,5*	5,7 ± 0,8* 8,7 ± 0,5* , **	10,4 ± 1,6 11,2 ± 0,4	8,8 ± 1,2 23,3 ± 0,6**
Ar (rel.unit)	–9,8 ± 1,1	1 2	–8,3 ± 0,9 –8,4 ± 0,5	–9,0 ± 0,9 –6,8 ± 1,5	–9,2 ± 0,9 –9,0 ± 0,2	–8,5 ± 0,6 –8,8 ± 0,2
Kk	22,8 ± 1,2	1 2	39,5 ± 4,3* 35,7 ± 2,0*	36,1 ± 2,4* 28,6 ± 1,8**	33,7 ± 2,5* 25,4 ± 1,2**	32,3 ± 2,3* 22,5 ± 0,9**

Notes: 1 — traditional ADP treatment without correction of hemostatic indicators; 2 — additional specific correction of hemostatic disorders; * — p < 0.05 as compared to control; ** — p < 0.05 as compared to traditional ADP treatment.

In the 2nd group of patients we followed the basic program of intensive therapy, including a meaningful specific correction of the hemostatic system disorders, making it differentiated, depending on the revealed clinico-pathogenetic variant of DIC-syndrome. Such-like modification gave positive effect — lethality reduced by 30.9%.

From the perspective of the results obtained, we devised the treatment policy to include the components as follows (Table 2): infusion-transfusion therapy with intensive circulating blood volume (CBV) during the first 12-24 hours, controlled by the central hemodynamics indicators and recovery of adequate hour-by-hour diuresis. CBV deficit reaches 40% in destructive forms of pancreatitis and is associated with a sharp plasma deficit.

From the perspective of organ impairments in acute destructive pancreatitis — in order to correct hypovolemia with controlled rheologic effect — we see it optimal to choose multicomponent, polyionic colloid hyperosmolar solution Gecoton, taking into account its upgraded safety profile, approved in numerous studies [9, 10].

Upon the study results (Table 3), Gecoton infusion in a dose of 400 ml was found to have the pronounced hemodynamic effect, elevating arterial pressure by 28-30 mm Hg, on an average. Hemostatic system indicators (records of LPTEG, APPT, PTI, fibrinogen, platelets) did not reflect substantial impact of Gecoton on hemostasis. Practical observations showed an ultimate drug efficacy in its early prescription, at the preoperative stage.

With regard for a complex approach to IT program, it should be recognized that the result obtained may be explained not only by the use of Gecoton, but also the program as a whole, upon condition of prompt and adequate surgeon's performance.

But the role of Gecoton — to form the "first defense line" against shock, to retain CBV before the threshold of irreversible hypovolemia, this giving time to make an accurate diagnosis and collect ingredients of infusion program.

In acute destructive pancreatitis (ADP), hypercoagulation is accompanied with the exhaustion of anticoagulative factors: AT III, protein C, components of fibrinolytic system — plasminogen and plasmin. With the purpose of their recovery, we believe it expedient to include into the complex of corrective therapy the freshly-frozen plasma (FFP), containing these components in optimal concentrations and ratios. To optimally activate AT III, FFP is supplemented with heparin (2500 U/250 ml of FFP).

More effective restriction of excessive platelet aggregation is achieved via using disaggregant Latren (200 ml/day).

In severe course of the disease and insufficiently rapid normalization of the basic hemostatic indicators, we deem advisable to prescribe protease inhibitors in combination with medicinal agent, reducing vascular permeability — dycinone. Additionally, therapeutic plasmapheresis is made, to promote the removal of toxic decay products and cellular aggregates, formed as a result of action of the primary disturbing factor, activated coagulative factors, fibrinogen degradation product — fibrin.

As a result of comparative analyses it was established that the efficacy of specific correction of hemostatic disorders depend on the pronouncement of clinical symptoms and signs. In severe course of the disease normalization of hemostatic indicators runs gradually, beginning from the first day since the treatment commencement, and distinctions with control become minimal after 5-7 days. After 3 days of intensive therapy, the condition of patients from the 2nd group was characterized by a define stability. In all patients, the pain syndrome was cut short to a considerable degree, diuresis recovered completely, vomiting stopped. Hematocrit in this group accounted for 0.34 ± 0.04 relative units (RU), number of platelets in the blood — 138.8 ± 25.6 • 109/l. The baseline Ar LPTEG indicator, characterizing the blood physical and chemical properties, was at the beginning of coagulation process close to its value in healthy persons and was to some extent the evidence of normalization of the blood rheological properties. Moderate chronometric hypocoagulation was registered by all indicators of LPTEG and coagulogram, this being explained by the ongoing heparin therapy.

Table 2. Specific correction of hemostatic disorders in destructive pancreatitis depending on clinico-pathogenic variant of DIC-syndrome course

Variant of DIC-syndrome course in the 2nd study group of patients	Correction of hemostatic disorders	Therapy duration
Coagulative variant of DIC-syndrome	Gecoton solution, 400 ml/day Heparin, 5 000 U, 6 times daily Latren, 200ml/day FFP, 3 ml/kg/day	7 days
Fibrinolytic variant of DIC-syndrome	Gecoton solution, 400ml/day Heparin, 5 000 U, 6 times daily Trasylol, up to 5,000.00 U/day Dicinone, 250 mg 4 times daily FFP, 3.5ml/kg/day In thrombocytopenia less than 50 000/μl – transfusion of platelet concentrate Therapeutic plasmapheresis	10 days and more

Table 3. Results of examining ADP patients before and after Gecoton infusion

Indicator	Before infusion	In 6 hours	In 24 hours
Pulse, b/min	121 ± 12	88 ± 4*	91 ± 3*
APav., mm Hg	71 ± 18	83 ± 6	94 ± 3*
CBV, ml/kg	53 ± 2*	52 ± 2*	54 ± 1,5*
Hemoglobin, g/l	81 ± 8	97 ± 4	113 ± 5*
Hematocrit, %	28,2 ± 2,0*	38,0 ± 1,8*	39,0 ± 1,2*
CVP, mm w.c.	15,0 ± 10,3	24,0 ± 5,1	50,0 ± 7,2

Noted was the increased incidence of pulmonary complications in the 1st group of patients as compared to the 2nd group — 71.9 versus 42.6%, respectively. Bed-day at the SRIT department in the 1st group amounted to 11.29 ± 0.67, in the 2nd group — 9.56 ± 1.64, at in-patient facility — 32.97 ± 3.11 and 25.42 ± 4.18, respectively.

Lethality in the 21st group was 6 (18.75%), in the 2nd group — 7 (12.96%) patients.

In terms of prognosis, it is necessary to take into account the fact that lethality decreased in the cases, where under the impact of specific correction, beginning from the 3rd day, normalized were the following indicators: early clot formation time (r), thrombin constant (k), clottage intensity (Kk), clot density (AM) and fibrinolytic activity (F).

Conclusions

1. Changes in hemostatic parameters in acute destructive pancreatitis are of multidirectional character: system unbalance from considerable hypercoagulation to clear hypocoagulative state even in the first hours of the disease, this being explained by the severity and rate of DIC-syndrome development. Directionality of these shifts largely differs, depending on the disease course severity. Formation of disorders is explained by pancreatic shock pathogenesis itself.

2. The use of the low-frequency, piezoelectric thromboelastography method (analyzer ARP-01) makes it possible to timely and rather adequately evaluate hemostatic disorders in acute period of destructive pancreatitis, with minimal material costs and within a short time, directly at the bedside. Prospective is the use of laboratory indicators in early diagnosis of pancreatic necrosis and when assessing the severity of patients' condition.

3. DIC-syndrome therapy in patients with acute destructive pancreatitis must be carried out under permanent monitoring of hemostasiologic parameters differentially, depending on the existing coagulation impairments.

4. Correlation of the results obtained, clinical observation and analysis literature data makes for a conclusion that multicomponent, polyionic, colloid hyperosmolar solution Gecoton is indicated as the basic infusion solution in intensive therapy of hypovolemic disorders in patients having acute destructive pancreatitis.

5. Specific correction of hemostatic disorders in acute destructive pancreatitis, with regard for pronounced clinico-pathophysiological manifestation via impacting on the key pathogenic factors by means of Gecoton, purpose-oriented prescription of heparin, Latren. Trasylol, freshly-frozen plasma, and therapeutic plasmapheresis enables the incidence of pulmonary complications to be reduced by 1.7 times, cuts the time of stay at in-patient facility by 23%, as well as decreases lethality in severe course of the disease by 30.9%.

List of literature

1. *Gelfand B.R., Filimonov M.I., Burnevich S.Z. et al. Evaluating the efficacy of different regimens of prophylaxis and therapy in pancreatic necrosis // Consilium medicum. Annex. — 2001. — 12-14.*

2. *Molchanov I.V., Bulanov A.Yu., Shulutko Ye.M. Some aspects of infusion therapy safety // Clinical anesthesiology and resuscitation. — 2004. — V. 1, No, 3. — P. 19-24.*

3. *Saveliev V.S., Gelfand B.R.., Filimonov M.I, Burnevich S.Z., Tsyderzhanov Ye.Ts., Orlov B.B. Comprehensive treatment of pancreatic necrosis // Annals of surgical hepatology. — 2000. — V. 5, No.2. — P. 61-66.*

4. *Tarabrin O.O. Complex correction of thrombohazard at the stages of surgical treatment // Bulletin of marine medicine — 1998. — No. 2. — P. 64-65.*

5. *Tarabrin O.A., Lobenko A.A., Zaporozhchenko B.S., Gozhenko A.I., Kyriliuk A.A. Method of integral evaluation of the hemostatic system functional condition // Clinical surgery. — 1998. — No. 7. — P. 30-32.*

6. *Chernii V.I., Kabanko T.P., Kuznetsova I.V. Disorders in the system hemostasis in critical states. — Kyiv: "Zdorovya" (Health), 2000. — 206 p.*

7. *Boldt J. Fluid management of patients undergoing abdominal surgery — more questions than answers // European Journal of Anaesthesiology. — 2006.*

8. *Cheng D. et al. Colloids for perioperative plasma volume expansion: systematic review with meta-analysis of controlled trials // Transfusion Alternatives in Transfusion Medicine. — 2007. — Vol. 9 (Suppl. 1). — S3.*

9. *De Jonge E., Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review // Crit. Care Med. — 2001. — V. 29, № 6. — P. 1261-1267.*

10. *Hoffmann J.N. et al. HES — 130/0.4 but not crystalloid volume support improve microcirculation duaring normotesive endotexemia // Anaesthesioligy. — 2002. — 57. — 463-470.*

11. *Nathens A.B., Curtis J., Beal R. et al. Management of critically ill patient with severe acute pancreatitis // Crit. Care Med. — 2004. — 32. — 2524-2536.*

12. *UK guidelines for management of acute pancreatitis // Gut. — 2005. — 54. — 1-9.*

Received: 24.03.14

Тарабрін О.О., Щербаков С.С.
Одеський національний медичний університет

ОСОБЛИВОСТІ ДІАГНОСТИКИ ПОРУШЕНЬ ГЕМОСТАЗУ І ОПТИМІЗАЦІЯ ІНФУЗІЙНОЇ ТЕРАПІЇ ПРИ ТЯЖКОМУ ПЕРЕБІГУ ДЕСТРУКТИВНОГО ПАНКРЕАТИТУ

Резюме. У роботі патогенетично обґрунтовуються і апробуються способи підвищення ефективності лікування деструктивного панкреатиту за допомогою експрес-діагностики і корекції порушень гемостазу, проаналізова-но клінічний досвід застосування багатокомпонентного, полііонного, колоїдно-гіперосмолярного розчину нового покоління Гекотон у комплексному лікуванні панкреатичного шоку. Дослідження проведено у 86 хворих із тяжкими формами ОДП. Стан системи гемостазу оцінювали за допомогою показників аналізатора АРП-01 «Меднорд» (низькочастотна п'єзоелектрична тромбо еластографія, НПТЕГ), класичними лабораторними тестами. Використання методу тромбоеластографії дозволило вчасно оцінити порушення гемостазу в гострому періоді деструктивного панкреатиту, з мінімальними матеріальними витратами в короткий термін, безпосередньо біля ліжка хворого. Специфічна корекція порушень гемостазу при деструктивному панкреатиті за допомогою впливу на ключові патогенетичні фактори за допомогою Гекотону, цільового призначення НПТЕГ із різним механізмом дії, Латрену, трасилолу, свіжозамороженої плазми й лікувального плазмаферезу дозволяє зменшити частоту легеневих ускладнень в 1,7 раза, скорочує час перебування в стаціонарі на 23 %, а також знижує летальність на 30,9 % при тяжкому перебігу захворювання.

Tarabrin O.A., Scherbakov S.S.
Odessa National Medical University, Odessa, Ukraine

FEATURES OF DIAGNOSIS OF HEMOSTATIC DISORDERS AND OPTIMIZATION OF INFUSION THERAPY FOR SEVERE DESTRUCTIVE PANCREATITIS

Summary. The paper pathogenetically substantiates and approves ways to improve the efficacy of treatment for destructive pancreatitis using rapid diagnosis and correction of hemostasis disorders, as well analyzes the clinical experience of application Gekoton, a multi-component, polyion colloid hyperosmolar solution of new generation, in the complex treatment of pancreatic
shock. The study was conducted in 86 patients with severe forms of acute destructive pancreatitis. The hemostatic system was evaluated using indicators of analyzer ARP-01 Mednord (low-frequency piezoelectric thromboelastography, LPTEG), classical laboratory tests. Using the method of thrombelastography enables to evaluate timely the hemostatic disorders in acute period of destructive pancreatitis, with minimal material costs in the short term, at the bedside. Specific correction of hemostatic disorders in destructive pancreatitis by acting on the key pathogenetic factors using using Gekoton, purpose use of LPTEG with different mechanisms of action, Latren, trasylol, fresh frozen plasma and therapeutic plasmapheresis can decrease the incidence of pulmonary complications by 1.7 times, reduces the duration of hospital stay by 23 %, as well as and reduces mortality by 30.9 % in severe course of disease.