Use of Plasmapheresis in the Enzymatic Phase of Severe Acute Pancreatitis

S. E. Khoroshilov[1,2], A. V. Nikulin[1,2], A. V. Marukhov[2]

[1] V. A. Negovsky Research Institute of General Reanimatology, Russian Academy of Medical Sciences, Moscow
[2] N. N. Burdenko Main Military Clinical Hospital, Ministry of Defense of the Russian Federation, Moscow

Objective: **to evaluate the efficiency of early plasmapheresis in the enzymatic phase of severe acute pancreatitis.** ***Patient characteristics and methods*****. Thirteen 25-to-86-year-old patients diagnosed with severe acute pancreatitis (SAP) were examined and treated at the intensive care unit of the military hospital (Sergiev Posad) in 2011—2012. The patients underwent comprehensive clinical, laboratory, and instrumental examinations. Their clinical and laboratory parameters were analyzed at admission, before and after extracorporeal detoxification. The exfused plasma level of pancreatic enzymes was studied. The admission patient status was assessed using the APACHE II; the severity of the disease was evaluated employing the Glasgow and Ranson pancreatic scales; the Murray scale was used to estimate the degree of acute lung lesion. During the prospective study, there were 2 patient groups: 1) 7 patients who underwent extracorporeal detoxification in early-stage disease (on days 1—2); 2) 6 patients received infusion therapy with forced diuresis elements as detoxification measures (a comparison group). The incidence of acute respiratory distress syndrome (ARDS), pancreatic tissue destruction, and pyoseptic complications and intensive care unit stay and hospital length of stay, and mortality were comparatively analyzed.** ***Results*****. The investigation demonstrated that there were reductions in the incidence of ARDS by 35.7%, pancreatic destruction by 35.7%, and pyoseptic complications by 16.7% and in the intensive care unit stay and hospital length of stay by 42.9 and 31.2%, respectively, and in mortality rates by 16.7% in Group 1 compared to Group 2.** ***Conclusion*****. The use of plasmapheresis to treat early-stage SAP assists in reducing the magnitude of enzymatic toxemia due to the direct elimination of pancreatic enzymes from systemic circulation. This sanogenic effect can offset the aggressive effect of hyperenzymia and hence prevent ARDS even in severe baseline disease. Early plasmapheresis allows the results of intensive therapy for SAP to be improved.** ***Key words:*** **severe acute pancreatitis, acute respiratory distress syndrome, plasmapheresis.**

Introduction

Despite recent advances in the study of pathophysiological aspects of the development and creation of pathogenetic methods for complex therapy, the treatment of acute pancreatitis and its complications is still a pressing problem in modern emergency medicine. Accounting for 12.5% of all urgent pathologies, AP (acute pancreatitis) ranks third among all acute surgical illnesses of the abdominal cavity [1]. The most severe form of the disease — destructive pancreatitis — can be found in 15—20% of the cases; mortality due to this disease reaches 21%. It should be noted that about 70% of AP patients are of working age (from 30 to 50 years), while the incapacity to work appears in 73.5% of the patients with acute destructive pancreatitis [2]. The question of treating AP is not only medical, but also one with a high social and economic significance.

The main component of the pathogenesis of acute pancreatitis is endogenous intoxication (EI), which is formed in the early stages of the disease, determines the severity of pathological changes in the patient's body, and causes high mortality [3].

One of the earliest and most dangerous systemic dysfunctions in the development of AP is ARDS (acute respiratory distress syndrome), which involves diffuse pulmonary capillary endothelial damage, accompanied by disorders of the aero-haematic barrier [4]. Secondary lung injury complicates AP in 30—35% of the patients, and, according to various estimates, the mortality rate caused by AP in the development of ARDS reaches 50—70% [5, 6].

Correspondence to:

Artem Vladimirovich Marukhov
E-mail: maruxov84@mail.ru

The leading role of pancreatogenic enzymes in the development of severe disorders of homeostasis and life-threatening systemic complications during the fermentation phase of AP necessitates the removal of these auto-aggressive factors from the internal environment of the body. Currently, the most effective methods of eliminating toxins from systemic blood circulation are operations using extracorporeal detoxification techniques [7, 8]. In the last decade, efferent treatment methods, such as haemosorbtion, lymphoplasmatic sorbtion, haemofiltration, and xenoperfusion, have been used in complex intensive therapy of acute pancreatitis [9]. Thanks to their effect on blood, lymph or plasma, all of these methods reduce the intoxication level in patients with AP. Despite the great variety of extracorporeal detoxification and haemocorrection techniques, most clinics use plasmapheresis [10, 11] and haemodiafiltration [12—14] to treat patients with AP; these methods are truly effective when used as an adjuvant therapy applied after initial treatment of AP [12, 14]. However, it should be noted that the range of substances, eliminated by detoxification techniques using prolonged filtration, are, in most cases, limited to low-and-medium-molecular-weight substances [7], whereas pancreatic enzymes, which are the most important predictors of acute lung injury in the early stages of AP, have a significantly greater mass. So, the molecular weight of lipase is 48 kDa, elastase — 28 kDa, trypsin — 24 kDa, and phospholipase A2 — approximately 15 kDa [15]. Highly aggressive factors, such as activated pancreatic enzymes, can be effectively removed from the internal environment through plasmapheresis [16]. Therefore, we consider it reasonable to conduct a research study in order to determine the effectiveness of plasmapheresis in reducing hyperenzymemia as one of the major pathogenetic factors of the development of AP and its complications, especially acute lung injury (ALI) as an early stage of ARDS.

Table 1

Baseline clinical and laboratory indicators in patient groups

Parameters, units of measurement	Value of indicators in groups		
	all patients (*n*=13)	1st (*n*=7)	2nd (*n*=6)
Age, years	47 (25—86)	50 (25—86)	44 (32—75)
APACHE II, scores	12 (9—20)	12 (9—17)	12 (9—20)
SOFA, scores	11 (8—15)	10 (8—15)	11(10—14)
Ranson, scores	8 (6—10)	7 (6—8)	8 (6—10)
Glasgow, scores	5 (3—8)	5 (3—7)	4 (3—8)
Murray, scores	0.3 (0—2)	0.4 (0—2)	0.3 (0—2)
Pancreatic α-amylase, u/l	1664 (254—2170)	1723 (346—2170)	1540 (252—1844)
Lipase, u/l	361 (63—576)	373 (86—576)	348 (63—498)
LII (leukocyte intoxication index)	1.9 (0.5—2.4)	1.9 (0.6—2.2)	2.0 (0.5—2.4)
AST, u/l	61 (23—121)	67(24—121)	56 (23—109)
ALT, u/l	52 (25—74)	58 (25—74)	49 (30—68)
Total bilirubin, mcmol/l	22.6 (16.1—29.4)	24.6 (16.1—28.8)	20.6 (17.6—29.4)
Glucose, mmol/l	10.5 (6.2—16.7)	11.2 (6.4—15.6)	10.0 (6.2—16.7)
White blood cells, $\times 10^9$/l	12.7 (8.8—14.7)	12.7 (8.9—14.7)	12.6 (8.8—13.8)
Haematocrit	0.49 (0.44—0.52)	0.48 (0.45—0.50)	0.49 (0.44—0.52)
Oxygenation index	354 (292—443)	367 (302—443)	335 (292—429)

Note. Here and table 2: the data are presented as a median and interquartile range.

Materials and methods

The study included thirteen patients aged 25 to 86 years; the median age was 47 years, including five women (38%) and eight men (62%), who were being treated in the intensive care unit of a military hospital (town of Sergiev Posad) in 2011—2012. The patients were diagnosed with AP based on the combination of clinical and laboratory data, ultrasound results, computer tomography of abdominal cavity organs, and the results of diagnostic laparoscopy. The severity of the patients at admission was evaluated according to the APACHE II scale, the severity of multiple organ dysfunctions according to the SOFA scale, the severity of the disease according to the Glasgow and Ranson scale, and the ARDS level according to the Murray scale. The dynamics of the severity of the patients' condition were evaluated daily according to the Glasgow, SOFA, and Murray scales. We made daily evaluations of indicators showing the acid-base balance in venous and arterial blood, the oxygenation index, clinical and biochemical blood tests (haemoglobin, haematocrit, red blood cells, white blood cells, platelets, total protein, albumin, total bilirubin, AST, ALT, urea, creatinine, fibrinogen, electrolytes), and urine levels; we examined pancreatic enzymes (pancreatic α-amylase, lipase) in the patients' blood serum and exfused plasma. ARDS was established through clinical and laboratory data, and radiological examinations of the thoracic cavity [17].

All patients underwent complex intensive therapy: infusion, antibiotics (Metronidazole, Cefepime), antifermental treatment, stress ulcer prophylaxis in the gastrointestinal tract, nutritional support by nutrient mixtures fed through a nasointestinal tube, prophylaxis for thrombotic complications (unfractionated heparin), and epidural blocks.

Two groups of patients were organized during the prospective study: the first group consisted of seven patients who underwent plasmapheresis in the early stages of the disease (1—2 days) with the removal of 30 to 50% of the estimated amount of circulating plasma by a centrifugal-type of apparatus — PCS-2 (Haemonetics, USA). The plasma exchange was carried out using the isovolemic mode with crystalloids, hydroxyethyl starch solutions, and freshly frozen plasma in a ratio of 1:1:1 with citrate anticoagulation. The control group consisted of six patients who underwent fluid therapy with crystalloids and colloid solutions (ratio 4:1) in the amount of not less than 40 ml/kg, with stimulation through intake of Furosemide and maintaining the speed of diuresis by not less than 2 ml/kg per hour.

A comparative analysis was conducted on the incidence of the development of ARDS, septic complications, the patients' length of stay in the intensive care unit and hospital, and the mortality rate.

The data, obtained in this research study, are presented as a median and interquartile range (25th and 75th percentiles). Non-parametric criteria were used to check statistical hypotheses (Kolmogorov-Smirnov test and Mann-Whitney test). The probability of a correct prognosis equal to 95% (p=0.05) was taken as the critical level of statistical significance. Statistical data processing was carried out using the statistical analysis software — BioStat 2009, AnalystSoft Inc.

Results and discussion

A comparative analysis of the major clinical and laboratory findings in patients from Groups 1 and 2 showed that the most important indicators in the study groups were not significantly different (Table 1).

The severity of the patients' condition and the severity of their illness in both groups were not statistically different and averaged 14.0 (9.0—20.0) scores on the APACHE II scale, and 5.0 scores (3.0—9.0) on the Glasgow scale; the severity of multiple organ dysfunction was recorded at 11.0 (8.0—15.0) on the SOFA scale. All patients were admitted to hospital no later than the second day after the onset of the disease.

Group 1 patients started extracorporeal detoxification within 48 hours after the onset of the disease. A total of 31 plasmaphereses were carried out, averaging 3.0 (1.0—4.0); the interval between these operations lasted 24 hours. The volume of plasma exchange averaged 42.7% (30—50%). Studies on the pancreatic enzyme levels in the patients' blood prior to and immediately after extracorporeal detoxification showed a reduction in pancreatic α-amylase by an average of 35.5%, and in lipase — by 40.2%. The dynamics of the indicators during the enzymatic phase showed significant differences in both groups:

The dynamics of the main clinical and laboratory parameters before and after plasmapheresis are presented in the table.

However, ALI (acute lung injury) was observed only in one Group 1 patient (14.3%) suffering from mild disease

Table 2

Dynamics of clinical and laboratory indicators after plasmapheresis

Parameters, units of measurement	Value of indicators on the stages of the research	
	before plasmapheresis (*n*=7)	after plasmapheresis (*n*=7)
Glasgow, scores	5 (3—7)	3 (2—5)*
Pancreatic α-amylase, u/l	1383 (224—1970)	1026 (84—1316)*
Lipase, u/l	378 (78—564)	251 (46—467)*
LII, studied units	1.9 (0.6—2.2)	1.6 (0.4—1.9)*
AST, u/l	66 (24—117)	45 (23—87) *
ALT, u/l	62 (29—80)	48 (25—61) *
Total bilirubin, mcmol/l	26.6 (16.8—32.4)	19.1 (15.3—25.8)*
Glucose, mmol/l	11.4 (6.5—16.0)	8.8 (5.4—12.0) *
White blood cells, $\times 10^9$/l	13.2 (8.7—15.1)	10.0 (6.9—12.7)*

Note. * — statistically significant differences (p<0.05).

Table 3

Incidence of complications in severe cases of acute pancreatitis

Parametrs	Complications in groups	
	1 (*n*=7)	2 (*n*=6)
Acute lung injury, *n* (%)	1 (14.3)	3 (50)*
ALV (artificial lung ventilation) required, *n* (%)	—	2 (33.3)*
Multiple organ failure, *n* (%)	—	1 (16.7)
Pancreatic destruction, *n* (%)	1 (14.3)	3 (50) *
Purulent septic complications, *n* (%)	—	1 (16.7)

Note. Comparison of differences (P<0.05, Mann-Whitney criteria) between the groups.

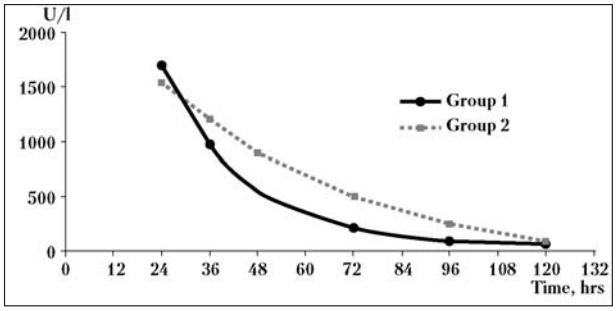

Fig. 1. Dynamics of pancreatic α-amylase levels in blood during the enzymatic phase of acute pancreatitis.

Here and Fig. 2: Statistically significant differences (P<0.05) between the groups from 36 and 84 hours after the onset of the disease..

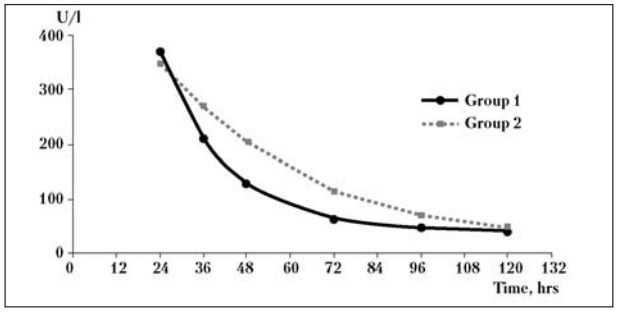

Fig. 2. Dynamics of lipase levels in blood during the enzymatic phase of acute pancreatitis.

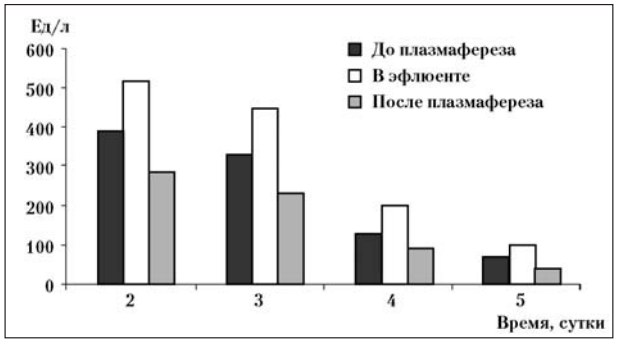

Fig. 3. Dynamics of lipase levels in blood of Group 1 patients before and after plasmapheresis.

Statistically significant differences (P<0.05) between lipase levels before and after plasmapherisis. with drawn plasma

(2 scores on the Murray scale). After two extracorporeal detoxification operations, the pulmonary dysfunction symptoms were eliminated. We remarked the progression of pancreatic destruction only in one patient. There were no purulent septic complications or deaths among Group 1 patients. The patients' stay in the intensive care unit averaged 4.0 (3.0—6.0) days; the total period of hospitalization was 11.0 (9.0—13.0) days.

We observed the development of ARDS in two Group 2 patients (33.4 %) during the enzymatic phase of the disease (4 and 10 scores on the Murray scale); their condition required artificial lung ventilation. One patient died as a result of the progression of multiple organ failure. We noted signs of moderate severity of ARDS in another patient (3 scores on the Murray scale). According to CT and ultrasound data, three patients (50.0%) were diagnosed with purulent septic complications in the form of a pancreatic abscess, phlegmon of the retroperitoneal space, and abdominal sepsis. The patients' stay in the intensive care unit and hospital increased compared to that of Group 1 patients, numbering 7.0 (5.0—11.0) and 16.0 (12.0—21.0) days, respectively.

When comparing Group 1 and Group 2, Group 1 showed a reduction in the incidence of ALI by 35.7%, pancreatic destruction — by 35.7%, septic complications — by

16.7%, patient's length of stay in the intensive care unit — by 42.9%, the hospital treatment period — by 31.2%, and the mortality rate — by 16.7% (Table 3).

In EI (endogenous intoxication), accompanied by AP (acute pancreatitis), excess substances enter and are preserved in the internal environment as a result of systemic impairments of the metabolism and inactivation disorders of metabolic products of natural detoxification systems in conjunction with an enormous output of inflammatory products, necrobiosis, and hypoxia [18]. EI is, therefore, a complex multicomponent process, which is conditioned by the abnormal activity of many endogenous products [5, 8]. However, in the early stage of AP, the most important pathogenic component of EI is enzyme toxemia — the result of activated pancreatic enzymes falling into systemic blood circulation. It is namely pancreatogenic enzymatic fermentation that constitutes the main cause of disorders of the homeostatic functions of the body at the onset of the disease.

The results of this research study demonstrate the effectiveness of plasmapheresis as part of complex intensive care during the enzymatic phase of AP. We demonstrated that there was an improvement in treatment, which consisted in reducing the incidence of life-threatening complications, such as ARDS. In our opinion, this therapeutic and preventive effect is associated with the removal of large molecular toxins, mainly activated by pancreatic enzymes, from the bloodstream. Enzymatic toxemia determines the severity of pathogenetic changes in the body during the early stages of the disease. Therefore, the removal of pancreatic enzymes from systemic blood circulation allows specialists to reduce the risk of organ dysfunction, which includes ARDS — one of the earliest and most dangerous pathological conditions. Significant difficulties in treating ARDS during AP, associated with the complexity of multifunctional and structural abnormalities and the lack of standardized approaches to therapy, lend increasing importance to preventing secondary lung injury in the early stages of the disease. We believe that plasmapheresis is effective in preventing ARDS, the use of which is justified during the enzymatic phase of AP.

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