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WAYS TO IMPROVE RESULTS OF TREATMENT IN DESTRUCTIVE PANCREATITIS

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The article is based on study and systematization of causes for death of 71 patients among 304 patients having acute destructive pancreatitis. Active surgical tactics was applied for the control group of patients (138), in the basic group of patients (166) the tactics of treatment was optimized by means of use of new technologies. The main principle for the basic group was refusal of early traditional operative interventions that led to reduction of fatal outcome more than a half as much (2.1).Early hospitalization and timely beginning of treatment, age and presence of associated diseases, volume of pancreatonecrosis, involvement of distant areas of spatium cellulosum, amount of systematic complications and optimized algorithm of treatment influenced fatal outcomes.

Keywords: acute destructive pancreatitis, complications, lethality

В статье изучены и систематизированы причины смерти у 71 умершего больного из 304 пациентов острым деструктивным панкреатитом. В контрольной группе больных (138) применялась активная хирургическая тактика, а в основной группе больных (166) тактика лечения оптимизирована за счет внедрения новых технологий. Главным принципом в основной группе явился отказ от ранних традиционных вмешательств, что привело к снижению летальности в 2,1 раза. На течение заболевания оказывали влияние сроки госпитализации и своевременное начало лечения, возраст и сопутствующие заболевания пациентов, объем панкреонекроза, вовлечение в воспалительный процесс отдаленных клетчаточных пространств, количество системных осложнений и оптимизированный алгоритм лечения.

Ключевые слова: острый деструктивный панкреатит, осложнения, летальность

Introduction

Currently treatment of patients with acute pancreatitis (AP) is one of the most important unsolved problems of emergency surgery. The number of patients with AP is steadily increasing and varies from 38 to 95 people per 100 000 in different regions of Russia [1,2].

According to hospitals of St. Petersburg AP takes the first place in the structure of acute surgical diseases of abdominal organs since 2000 reaching 44.5% in 2006 (in absolute numbers — 11,250 people.) [3].

In 15-25% of patients AP is destructive [4,5]. In these cases patients represent the most severe (in the diagnostic, therapeutic, social and economic aspects) group of patients as evidenced by high rates of mortality, morbidity, hospitalization terms and financial costs, that were identified in analysis of cases of treatment for this serious disease.

Mortality from destructive pancreatitis (DP) without differentiating its variable clinical forms and stages was 22,7-23,6% in Russia and 26,2-28,3% in Moscow [4,6]. For spread forms of destructive pancreatitis mortality is within 30-50% [1, 7]. These findings differ little from those of foreign researchers, according to which the mortality rate for necrotizing pancreatitis ranges from 27-45% [5,8]. Total mortality from AP varies from 5 to 10% depending on the proportion of its severe forms.

Despite the improvement of pathogenetically directed intensive care the structure of mortality from severe pancreatitis has changed little. As 20-30 years ago almost half deaths occur in early phase of pathological process and 50 — 60% of patients die in late stages of the disease due to development of septic complications [9-11].

The high frequency of deaths first of all is evidence of ineffectiveness of treatment of patients with DP with multiple organ dysfunction syndrome (MODS) and pancreatic shock (PS) in toxemia phase. In addition the necessity to prevent infection and prompt diagnosis of developed complications in purulent-septic phase of destructive pancreatitis is evident [12-14].

Wide range of variation of total and postoperative mortality from AP in most cases is due to several reasons: late diagnosis of acute pancreatitis and its complications, lack of unified and coherent views on the form of disease, classification, assessment of severity and prognosis, lack of objective pathogenetic criteria for treatment tactics and variety of conservative and surgical methods of treatment in patients with DP [4,7].

Materials and methods

The research is based on results of examination and treatment of 1,242 patients with AP between 1991 and 2007. Breakdown of patients in groups and periods of observation is in Table 1.

Table 1

Breakdown of patients with AP according to forms and groups of disease, extent of necrosis and severity of condition

Form of pancreatonecrosis	Scale of severity		Quantity of patients in groups		Total Abs. (%) n = 304
	APACHE II (M±m)	Ranson (M±m)	control n = 138	basic n = 166	
Focal PN	8,4±1,2 [7-11]	4,5±1,3 [3-5]	74	85	159 (52,3)
Massive PN	14,1±1,3 [12-16]	6,3±1,2 [5-7]	44	57	101 (33,2)
Total-subtotal PN	18,5±1,5 [17-20]	9,5±1,4 [8-11]	20	24	44 (14,5)

There was no death cases in patients with edematous form of OP. Depending on the applied treatment patients were divided into 2 groups. The control group consisted of 138 patients with DP who had been treated in period from 1991 to 1999. Clinical material of this period formed the basis for analysis of therapeutic tactics and searching ways to improve it. Treatment of patients with destructive pancreatitis has been carried out according to tactics of early surgical intervention with using of extensive laparotomy.

Retrospective analysis of clinical material of the first period showed that the choice of surgical approach based on clinical and morphological criteria was not objective. From our point of view this fact is significant shortcoming of applied medical tactics, because they do not take full account of the severity of the disease. In addition during this period of observation we have not yet had clear criteria for prognosis of the disease that make it difficult to choose appropriate time for surgical intervention for each individual patient.

The second period of observation of 2000 – 2007 contained 166 patients (basic group) with different forms of DP. During this period of observation optimized tactics of examination and treatment of patients with DP based on forecast of the disease, antibacterial drugs and modern technologies surgery (laparoscopy, endoscopic papillosphincterotomy, minimally invasive methods of drainage of limited purulent complications of pancreatic necrosis) has been used.

The average age of patients in control group was 49,3 ± 7,1 years, in basic group — 47,2 ± 6,3 years. Persons of working age have prevailed among patients: 70.3% in control group and 75.3% — in basic group. As for patients older than 60 years control group contained 29.7% of them, basic group — 24.7%. Associated diseases, among which pathology of cardiovascular (70.2%) and respiratory (36.7%) systems was leading, significantly burdened condition of patients and complicated postoperative period.

Diagnosis of pancreatic necrosis (PN) and its various complications was verified basing on recommendations of IX All-Russian Congress of Surgeons. To assess the severity of patients conventional integral scale systems (Ranson, APACHE II) has been used. Patients with DP have been treated in intensive care department.

224 (73.6%) patients of 304 patients with DP underwent operation, including 121 (54.4%) patients with infected forms of pancreatic necrosis. Deaths were ascertained in 71 cases (23.3%).

Table 2 shows that 26 (36.6%) patients died in phase of pancreatogenic toxemia, pancreatic shock (PS) and multiple organ dysfunction (MOD).

Table 2

Breakdown of patients with AP according to causes of death

Causes of death	Quantity of observations	
	Abs.	%
Pancreatogenic shock and multiple organ failure	26	36,6
Pyo-destructive complications	33	46,5
Thrombohemorrhagic complications	12	16,9
Total	71	100

We carried out detailed retrospective analysis of cases of all patients who died from pancreatic necrosis. In all cases autopsy was performed to clarify nature of complication and cause of death. In the majority of cases the mixed form of haemorrhagic pancreatic necrosis with total or subtotal lesion of the pancreas (pancreatic) has occurred.

Analysis of mortality was conducted to study and systematize the causes of death in patients with subsequent correction of diagnostic and treatment process allowing preventing similar failures in future.

Results of the research and discussion

Own observations and literature data show that mortality rates depend essentially on the following key factors: terms of beginning and volume of treatment, the proportion of patients with destructive forms in total number of patients with AP, the volume (area and depth) of lesion of pancreas and surrounding fatty spaces, age and comorbidity, the frequency and nature of complications.

According to modern understanding of pathogenesis AP is time process which presents change of phases and periods with pathomorphological and pathophysiological features. It is the phase character of AP which enables logically to explain the reasons of manifestation and features of complications and their influence on outcome of DP. Terms of appearance and character of complications of DP are also different. These features form the basis of analysis of causes of death in the different phases and periods of disease.

Effect of complications on course of pathological process is differently. It was established that in one third of patients who died the cause of «early» death was pancreatogenic toxemia. This circumstance dictates the need for further improvement of methods of treating PS and MODS. Complications of the disease are caused by entering activated pancreatic enzymes (trypsin, lipase) and associated inflammatory mediators and other kinins (histamine, serotonin, bradykinin) to bloodstream that cause severe disturbances of microcirculation and central hemodynamics and therefore lead to dystrophic and necrobiotic changes in organs. The most typical complications in patients who died in early period (up to 7 days) were enzymatic destruction of serous membranes (enzyme-hemorrhagic peritonitis — 76.9%, pleuritis — 19.2%, pericarditis — 7.6%) as well as damage of fatty spaces (aseptic necrosis of parapancreatic – 88.4% and retroperitoneal fat — 76,9%), pulmonary edema — 38.5%. In essence these lesions are components of severe AP but they can be conditionally regarded as complications, since not all patients have them, and it worsens course of disease and require special treatment. Taking into account leading role of enzymatic toxemia and «cytokine storm» in pathogenesis of pancreatic necrosis effective detoxification is necessary to prevent development of shock. Our experience indicates that maximum efficiency of extracorporeal methods of detoxification is achieved only early used (with 1-2 days from admission to hospital), while the exchange plasmapheresis should be at least 1 volume of circulating plasma (VCP).

When analyzing results of primary examination of patients with AP it was revealed that only in 80.2% of all cases diagnosis of AP was established immediately in reception ward. If you mistakenly set primary diagnosis and underestimate severity of patient with ADP death ascertained in 50% of cases. Diagnosis of disease was difficult in significant part of deceased patients at admission to hospital.

Diagnostic mistakes at initial examination significantly influenced terms of beginning of intensive therapy. More than half death cases (56.3%) patients were hospitalized late to intensive care unit (ICU). This circumstance confirms the fact that the time period for beginning of adequate intensive therapy that can stop progression of pancreatic necrosis is very short.

Thus, late diagnosis, underestimation of patient's condition and tardy start of adequate therapy are serious problem and apparently one of the main reasons for failure in treatment of patients with DP.

Because of frequent lack of convincing ultrasound picture of DP (false-negative ultrasound picture at admission occurred in 33.3% of cases) and significant increase of amylase at initial examination (accuracy of rate was 50%), it is necessary to use additional tests. As marker of pancreatonecrosis in the second period test of C-reactive protein has been used, threshold of which is 150 mg / l and the accuracy of this test reaches 93%.

In the most difficult for diagnostics situations computed tomography has been performed in the second period of research, which is the most accurate method in diagnosing the form and scale of pathological process in pancreas and detection of intra-and extraperitoneal complications.

If group all patients with DP incidence of shock was 15%, then in deceased patients the frequency of shock in combination with MOD reached 36.6%. In third of cases of deaths patients were admitted to hospital with fully developed clinical picture of progressive or irreversible stage of shock. In other observations shock often developed due to late intensive care. Paramount importance in improving of treatment outcomes of pancreatonecrosis, besides timely diagnosis, is early prediction of disease severity, which was conducted in intensive care by scales of Ranson and APACHE II. Basing on evaluation of severity of patient's condition timely corrected volume infusion therapy, antibiotic therapy tactics have been corrected and terms of diagnostic and therapeutic procedures have been clarified.

Complications. Most of deceased had from 5 to 11 complications which led to poor outcome of pathological process. The immediate cause of death according to autopsy results was due to following complications: pancreatogenic shock and multiple organ failure, purulent-destructive and thrombohemorrhagic processes (Table 3).

Table 3

Complications of DP basing on results of pathological and anatomical research

	Complications	Quantity of observations	%
1.	Caused by endogenous intoxication:		
	- pancreatogenic shock	16	22,5
	- syndrome of multiple organ failure	10	14,1
2.	Thrombohemorrhagic complications		
	- haemorrhagic	6	8,5
	- thrombotic	6	8,5
3.	Septic complications:		
	- parapancreatic abscesses	11	15,4
	- retroperitoneal phlegmon	15	21,2
	- sepsis	7	9,8
	Total	71	100

In analysis of all complications it is worth to mention high incidence of pneumonia (35%) in patients with lethal outcome, which however was not direct cause of death. It should be noted that pneumonia often developed in early period in patients who died (already on the 1st week its rate was 15%). Cause of pneumonia was as severe lung lesions that are typical for PN and procedure of artificial lung ventilation itself (ALV), which increases the risk of developing pulmonary infection. Prolonged ALV for more than 24 hours is the most significant risk factor for nosocomial pneumonia in patients with PN. Developing arterial hypoxemia in 1 / 3 of patients with DP caused necessity to correct respiratory failure by performing ALV. Decreasing of partial pressure of oxygen in the blood (pO2) less than 60 mm Hg, saturation (SaO2) below 90%, increasing of respiratory rate more than 25 per minute are indicators for ALV in patients with destructive pancreatitis. Therefore it is advisable to make tests of gas content of arterial blood every 12 h in patients with DP during the first days of hospitalization. All patients being on prolonged ALV more than a day need an additional prevention of endogenous and exogenous infections [2]. For this purpose daily sanitation bronchoscopy with inoculation and bacteriological study of samples from lower respiratory tract, constant aspiration of secretion from overballoon space, processing of oropharyngeal with antiseptics, X-ray control of lungs have been performed every 3 days.

Among the other factors of poor outcome of DP patient age should be noted. The share of elderly in deceased group was 52% (37 patients) which is two times more than their share in the total group of patients with DP (26.9%). The high frequency of comorbidity in this age with dominated pathology of cardiovascular and respiratory systems leads to significant complications in patients and adversely affects postoperative period. Decompensation of cardiac and pulmonary diseases led to death in 1 / 3 of patients.

It is important to note that in nearly half lethal cases (34 pers. (48%)) death was ascertained at people of working age. This circumstance makes the issues of treatment of patients with DP socially significance.

Thrombohemorrhagic complications in patients who died because of AP were registered with the same frequency as in period of toxemia and in the period of destructive complications. These types of complications were stated in 35 (49.2%) cases. About 2 / 3 of hemorrhagic complications were bleeding from acute ulcers of the gastro-intestinal tract — 10 (14%) and retroperitoneal arrosive vessels — 13 (18.3%), while in 5.6% of death cases they were immediate cause death. After detecting of acute ulcers of gastrointestinal tract (GIT) bleeding prophylaxis should be done with using of the most effective drugs — blockers of proton pump parenterally (omeprazole, pariet, losek, kvamatel). In addition measures for improving tissue perfusion which is major cause of ulcer formation are obligatory.

The risk of acute gastrointestinal ulcers in patients with DP is accompanied with tendency to hypocoagulation and thrombocytopenia. In 25% of deaths among patients who were admitted to hospital deviations of hypocoagulation type have already been registered. Further these disorders have got worse and all time of hospitalization risk of hemorrhagic complications increased to 36.3%. Platelet decreased to less than $100 * 10^9$ / l in some patients averaging $(90 \pm 7) * 10^9$ / l. Steady hypercoagulation and thrombocytosis that occurred in lethal destructive pancreatitis was much less — in 5.6% and 2.8% of cases respectively.

12 (16.9%) of deceased patients had DIC. Its first phase, phase of hypercoagulation, was identified rarely,

probably because of its brevity. Changes characterized for subsequent phases of DIC are usually not treated as DIC and therefore targeted therapy has not been carried out. Transfusion of fresh frozen plasma (FFP) although was quite common, but was in much smaller amounts than it was recommended in treatment of DIC.

Thromboembolic complications occurred much more rarely than haemorrhagic. In case of pancreatonecrosis pulmonary embolism (PE) has been observed only in 2.8% of cases and thrombosis of splenic and portal veins — also in 2.8%. Artery thrombosis, particularly superior mesenteric, has been identified only in two cases (2.8%) against the background of hypercoagulation.

Reducing risk of thrombohemorrhagic complications is possible only with complex prophylaxis that aimed to both prevention and treatment of DIC and at the same time prevention of acute ulcers. Thrombocytopenia against the background of classical subsyndromes of DIC (respiratory insufficiency, acute ulcer, diffuse bleeding from mucous membranes) is considered to be sufficient to confirm diagnosis of pancreatic necrosis. When identified DIC requires specific therapy: transfusion of FFP (not less than 750-1000 ml per day to replace deficiency of clotting factors), physiological anticoagulants and plasminogen. Less intensive therapy is not able to reduce mortality in DIC. Trombocytosis and persistent changes in coagulation according t hypercoagulation are absolute indication for anticoagulation in case of DP.

12 of 35 patients died because of thrombohemorrhagic complications. Death occurred from tromboembolism of pulmonary artery (2), arrosive bleeding (4), DIC (2), thrombosis of splenic and portal veins in one patient and thrombosis superior mesenteris artery in two patients.

Pyo-destructive complications of DP were cause of death in 33 patients. The unfavorable factors of the disease are spread forms of pancreatic necrosis (Table 4). The prevalence was estimated by number of zones of retroperitoneal fat involved in process. Among them the retroperitoneal fat: parapancreatic, perirenal, paracolic spaces and pelvis and mesentery of small and large intestines can be distinguished.

These data show increase of lethal outcomes with increasing of number of affected anatomical areas of retroperitoneal fat among the dead from PN, MOD and pyo-destructive complications, especially with involving in process of three or more zones. It is clear that the large mass of necrosis provides massive toxin production and absorption of toxic products of decayed tissues, greater opportunities for infection and abscesses. Therefore patients with DP with lesions of three or more anatomic areas of retroperitoneal fat require more active disintoxication therapy during MOD. In these same patients more attention should be paid to antibacterial, immune therapy and other methods of prevention of septic complications and we should be prepared for surgical procedures in case of progression of destructive process or signs of suppuration.

Complications of infectious nature are typical for period of purulent complications of DP. Phlegmon of retroperitoneal fat has been verified in 70.4% of deceased patients, abscesses of different locations — 29.5%, diffuse fibropurulent peritonitis — 26.7%. Sepsis was cause of death in 19.8% of deceased. Combination of complications is typical. Cases of pneumonia in late period are more common than in early one and were verified in 20% of deaths.

In the majority of cases death in DP in late stages of disease probably indicates inadequate and often delayed surgical sanitation of septic foci.

Prompt diagnosis of septic complications of PN presents serious problem. Its successful implementation is impossible without using of modern techniques such as fine needle puncture of accumulated fluid under ultrasound with native microscopy and microbiological diagnosis. Test for procalcitonin is accepted throughout the world as marker of infection from all laboratory methodologies. Procalcitonin should be determined in all patients with spread forms of pancreatonecrosis. Beginning from the 10^{th} day of disease positive test indicates high risk of infection (in cases without clear clinical improvement). Test for procalcitonin should be repeated every other day. The threshold is 1.8 ng / ml and above.

46 (33.3%) patients of control group and 25 (15%) of basic one died. Using of optimized tactics of diagnosis and treatment by means of new technology helped to reduce mortality from DP in 2.1 times ($p < 0,001$).

Table 4

Breakdown of deaths from AP taking into account spread inflammation in retroperitoneal fatty space

Cause of death	Quantity of observations	%	Quantity of observations with involving of retroperitoneal fatty space to inflammatory process				
			one	two	three	four	five and more
Pancreatogenic shock and syndrome of multiple organ failure	26	36,6	—	3	8	7	8
Pyo-destructive complications	33	46,5	5	4	4	15	5
Thrombohemorrhagic complications	12	16,9	4	2	4	2	—
Total	71	100	9	9	16	24	13

Conclusion

Thus mortality rate from DP depends on terms of hospitalization and prompt treatment, age and comorbidities of patients, size of pancreatic necrosis, involvement in inflammatory process of remote fatty spaces, number of systemic complications and optimized algorithm for treatment. Excluding these criteria of prognosis and outcome of disease achievement of adequate quality of care in destructive pancreatitis is problematic.

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