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Modern Therapeutic Approach of Acute Severe Forms of Pancratitis. A Review of the Literature and Experience of Surgical Department No III Cluj

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Rezumat

Abordarea terapeutică modernă a formei severe a pancreatitei acute. Review al literaturii şi experienţa Clinicii Chirurgie III Cluj

Titulatura de "marea dramă abdominală" atribuită pancreatitei acute este pe deplin justificată de tabloul clinic impresionant, caracterul profund consumptiv al proceselor fizio-patologice care se derulează, severitatea complicaţiilor pe care le antrenează şi complexitatea tratamentului.
Material şi metodă: Scopul studiului nostru a fost analiza propriilor rezultate pe un număr de 81 de pacienţi consecutivi internaţi în Clinica Chirurgie III Cluj pe perioada a 28 de luni, toţi diagnosticaţi cu forma severă a pancreatitei acute, cu raportatea acestor rezultate la literatura de specialitate şi găsirea unor soluţii de ameliorare a lor. Bolnavii au fost împărţiţi în două loturi, neoperaţi (43 cazuri) şi operaţi (38 cazuri). În stabilirea diagnosticului şi a formei de boală s-a ţinut cont de tabloul clinic, valorile serice ale amilazelor, CPR şi procalcitoninei şi clasificarea Balthazar a leziunilor la examenul CT.
Rezultate: Toţi pacienţii au fost internaţi pe secţia de Terapie Intensivă, iar tratamentul de susţinere administrat a cuprins antibiotice, inhibitori ai secreţiei pancreatice exocrine şi ai pompei de protoni. Intervenţia chirurgicală (38 de cazuri) s-a indicat atunci când bolnavul a devenit septic sau atunci când presiunea intraabdominală mare ameninţa funcţionalitatea viscerelor vitale. Intraoperator s-au drenat abcesele, s-au înlăturat zonele necrotice şi s-a efectuat colecistectomia, la pacienţii cu etiologie biliară. Statistic, am obţinut diferenţe semnificative în ceea ce priveşte frecvenţa de apariţie a complicaţiilor între lotul bolnavilor operaţi şi cel al celor neoperaţi (p=0.000048), dar nu şi vis-à-vis de durata spitalizării (p=0.99999) şi numărul de decese (p=0.2102). Mortalitatea globală a fost de 14,41%, comparabilă cu cea regăsită în literatură. La nici unul dintre pacienţi nu s-a efectuat drenajul CT ghidat al colecţiilor înainte de intervenţia chirurgicală, acesta fiind neajunsul major al tratamentului pe care l-am aplicat.
Concluzii: Rezultatele noastre vin să susţină ideea importanţei diagnosticului şi a tratamentului medicamentos precoce, precum şi ideea intervenţiilor chirurgicale tardive, impuse de instalarea sepsei sau de presiunea intraabdominală mare.

Cuvinte cheie: pancreatita acută, forma severă, tratament medicamentos, intervenţii chirurgicale tardive

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Abstract

The title of "the great abdominaldrama" attributed to acute pancreatitis is fully justified by the impressive clinical presentation, the deep consumptive character of physio-pathological processes taking place, the severity of the complications and the complexity of the treatment.
Materials and methods: The aim of our study was to analyze the results on a number of 81 consecutive patients hospitalized in

the Surgical Clinic III Cluj during 28 months, all diagnosed with severe forms of acute pancreatitis. There were two groups of patients, non-surgical (43 cases) and surgical cases (38 cases), respectively. The diagnosis and forms of the disease took into account the clinical picture, serum amylase, CPR and Balthazar procalcitonine,together with the classification of the lesions on CT scan.

Results: All patients were admitted to the intensive care unit and received supportive treatment such as antibiotics, pancreatic exocrine secretion inhibitors and proton pump inhibitors. The surgical act in the 38 cases was indicatedby septic intra-abdominal pressure or high functionality threatening vital viscera. Intraoperatively the abscesseswere drained, the necrotic areas were removed and cholecystectomy was performed in patients with biliary etiology. Statistically, we obtained significant differences in the incidence of complications between the group of patients operated and those not operated ($p = 0.000048$), but not in what concerns the length of hospitalization ($p = 0.99999$) and the number of deaths ($p = 0.2102$). The overall mortality was 14.41%, comparable to that found in the literature. In none of the patients CT guided drainage of collections was performed prior to surgery, which was a major drawback of the treatment.

Conclusions: Our results support the importance of an early diagnosis and medical treatment, the delayed surgery being required in high intra-abdominal pressure or SEPS.

Key words: acute pancreatitis, severe form, medical treatment, latesurgery

Introduction

Acute pancreatitis reports an incidence varying from one country to another, between 5-100 cases/ 100.000 population (1,2,3,4,5), explainable by the unequal distribution of the principal risk factors of the disease, such as gallbladder stones and exessive consumption of alcohol.

20% of the patients with acute pancreatitis develop severe forms of the disease, characterized by local evolution of the disease towards necrosis and superinfection, and systemic through the appearance of multiple organ failure. The mortality in this severe form of acute pancreatitis is 7-15% (6,7). This percentage increases substantially with the presence of multiple organ failure. In this way, the mortality rate of patients with severe acute pancreatitis accompanied by respiratory, renal and hepatic insufficiency is 43%, 63% and 83%, respectively (8).

The prognosis of the patients depends mainly upon introduction of an early and correct treatment.Hospitalization in an intensive care unit is mandatory along with monitorization and sustainance of vital parameters,broad spectrum antibiotherapy, inhibition of exocrine pancreatic secretion and proton pumps, keeping a constant view that the surgical intervention is only indicated when the ultrasound-guided or CT-guided percutaneous drainage of the peripancreatic fluid collection is inefficient and when raised intraabdominal pressure poses a threat to the normal function of kidneys, lungs and heart. (9)

All these therapeutic measures are meant to prevent complications.Modern treatment strategies have the goal to modulate the exagerated inflammatory response and the CARS syndrome (anti-inflammatory response syndrome), by acting at the biological and physiological level of the cell, and improving the methods which allow us to identify potentially unfavourable evolution of the patient as early as possible.

Material and Method

Our study includes a number of 81 patients (24 female, 57 males; median age: 55.3 years, varying within 19-90 years), admitted to the Surgical Clinic No. III Cluj from January 2009 to April 2011, and diagnosed with severe acute pancreatitis. Out of all these patients, 38 (46.91%, 6 females, 32 males; median age 56.63, within the range 25-90 years), needed surgical intervention because of the evolution of the disease towards sepsis. The diagnosis was based upon the clinical finding supported by paraclinical investigations, serum and urinary levels of amylase and the imaging aspect (Ultrasound and CT).Severe acute pancreatitis was defined according to the Atlanta criteria (10). The CT results were included in the Balthazar clasification (11). The etiology of pancreatitis was found to be biliary in 35 cases (43.20%), alcoholic in 30 cases (37.04%), metabolic in 10 cases (12.35%) and the rest were found to be a mixed etiology like post-ERCP or idiopathic (7.41%). (*Table 1*)

Statistics

The data were analiysed from the statistical point of view and the results were expressed as a numerical form and as percentage, mean and standard deviation were utilised for continuous variables. Fischer test was utilised for the analysis of the data and a p-value lesser than 0.05 was considered to be statistically significant.

Results

Al the patients with severe forms of acute pancreatitis were admitted to the intensive care unit. Daily monitoring of the

Table 1. *Demographic data of the patients included in the study*

	Cases of acute pancreatitis (81)	**Cases of operated acute pancreatitis (38)**
Females	24(29.62%)	6(15.78%)
Males	57(70.37%)	32(84.21%)
Median age (years)	55.3	56.63
with limits between (yers):	19-90	25-90

general status, temperature, diuresis, intestinal transit, biochemical and hematologic parameters were performed. Imagistic investigations were performed whenever considered necessary. The CRP and procalcitonine levels were assayed dinamicaly.

The initial treatment was conservative and included reestablishing hydroelectrolitic balance, antibiotics (Tienam or Cephalosporines with Metronidazol), inhibitors of the exocrine pancreatic secretion (Sandostatin), inhibitors of the proton pumps. The patients were given both enteral and parenteral nutrition.

The surgical intervention was decided when the general status of the patient got altered by the appearance of sepsis, confirmed through increased leucocytes level, CRP and procalcitonine in the presence of an intraabdominal fluid collection found on CT or when the increased intraabdominal pressure threatened the functioning of the vital organs. The earliest surgical intervention was performed on day 6 and the latest was on day 22 during the evolution of the disease.

Intraoperatively there were performed necrosectomy, evacuation of the intraabdominal abcesses, peritoneal lavage and placement of the multiple intraperitoneal drainage tubes. In the case of the patients where the etiology was found to be biliary, colecistectomy accompanied other surgical manoeuvres (17 cases). Choledocotomy and external biliary drainageof the common bile duct were performed in case of these patients having hepato-coledochal lithiasis and in whom sfincterotomy and endoscopic drainage could not be performed earlier (5 cases) or were proven to be inefficient (3 cases). The latter were patientswho required an early surgical intervention to remove the causing factor. An open surgical method was used in all the cases because or the presence of multiple intraabdominal abcesses and the altered clinical status of the patients.

Postoperatively, the general status of the patients was monitored clinically and paraclinically, providing sustainance of the vital functions and antibiotherapy according to the antibiogram. A number of 16 patients out of the total who underwent the first surgical intervention had a favourable evolution, however 22 had complications, out of which 8 needed reintervention.

The most frequent complications were pancreatic fistulas (15 cases) and septic shock (4 cases). 6 patients (13.95%)of the group who did not undergo surgical intervention developed complications like MSOF.

Statistics obtained a significant difference between the group of patients who underwent surgery and the ones who did not undergo surgery, when it comes to the frequency of appearance of the complications.

Out of those patients who had a reintervention, 4 of them (50%) died. The reinterventions were performed within a period of 7-12 days from the first surgery, the surgical indication being the reappearance of the intraabdominal fluid collections. At the time of the reintervention, along with the evacuation of the intraabdominal collection, necrosectomy was performed whenever necessary.

In the case of 4 patients (9.30%) death occured in the first days of the disease due to multiple organ failure, and to be mentioned, and they belonged to the non operative group.

Table 2. *Evolution of the cases*

	Cases of nonoperated acute pancreatitis	Cases of operated acute pancreatitis	p
Complications	6 (13.95%)	22 (57.89%)	0.000048
Hospital stay (days)	11.48±9.43	30.89±23.38	0.99999
Deaths	4 (9.30%)	8 (21.05%)	0.2102

The global rate of mortality was 14.41%, 9.30% in those patients who did not undergo surgery and 21.05% in those who did have a surgical intervention. The median duration of hospitalization was 11.48±9.43 days for the unoperated cases and 30.89±23.38 days for the operated cases, respectively. We did not observe any significant difference in duration of inhospital stay (p=0.2102) and the mortality rate between the operated and non-operated patients (p=0.99999). (*Table 2*)

Discussions

Nowadays, acute pancreatitis is considered to be a systemic disease, as after activation of intraglandular pancreatic proteasis, followed by destruction of cellular membranes of the acins and liberation of the enzymes in the peripancreatic tissues, the body activates local protective mechanisms, like inflammatory reaction and activation of cytokines, events which can get out of the local control, resulting in uncontrolled, excessive activation of inflammatory cells and mediators, situation that is defined as SIRS (systemic inflammatory response syndrome) (12). Proinflammatory cytokines like TNF-α and IL-β are released in the circulation, through the portal vein (13), increasing the inflammatory response, and IL-6 stimulates the hepatic synthesis of acute phase proteins (CRP, procalcitonine) (14). Proinflamatory cytokines increase the capillary permeability of the entire organism, amplifying fluid loss and favouring intratissular migration of leucocytes (12), with the activation of neutrophiles and monocytes, which liberate the proteolitic enzymes and free radicals, destroying the vascular endotelium as well as the parenchimal cells (15). This phenomenon, accompanied by the defficiency of cellular oxygen, leads to the disfunction of vital organs, followed by their failure, most affected being those having rich capillary capital, like the lungs and the kidneys (15,16,17). Progression of events explaines the early deaths in acute pancreatits (12).

Concomitantly along with SIRS, with a role of controlling its magnitude, mechanisms of CARS (compensatory anti-inflamatory response syndrome)are occuring, but its exacerbation leads to immunosupression and an increased risk of infectious complications, in this way a characteristic feature of the later phase of the evolution of patients having acute severe pancreatitis (12,18). The most powerful anti-inflammatory cytokines are IL-10, responsible for the decreased monocyte HLA-DR expression (19). Along with the IL-10, in response to the immunosupression IL-1

receptor antagonist (IL-1ra) alsointervenes, which blocks IL-1 and IL-6.Although IL-6 was recognized for a long period of time as proinflammatory mediator, it was proven that it blocks the synthesis of IL-1β and TNF-α (20,21).

Knowledge of the mechanisms of CARS also has a practical aspect, as the plasmatic levels of the mediators have a predictive value.In this way, increased levels of IL-10 are specific for the severe form of acute pancreatitis andanticipates MSOF from the very beginning of the debut of the disease (22,23) and again decreased monocytes HLA-DR expression is associated with an increased risk of septic complications, MSOF and death (12).

Death in the later phase of acute severe pancreatitis is due to infectious complications secondary to immunosupression caused by exacerbation of CARS.

The review of the phenomenons generated by acute inflammation of pancreatic parenchyma has an important role to underline the importance of the early diagnosis of the disease, form of the disease and initiation of an adequate treatment, adapted to the dynamic pathological processes.

According to the Italian Association for the Study of the Pancreas, the diagnosis of acute pancreatitis has to be established in the first 48 hours of the hospitalization (24), based upon the clinical data supported by increased levels of serum amylase and lypase, and the CT aspect. The severity of the disease is established according to the APACHE II score (25). It can be used the serum level of CRP if it is not possible to measure the level of cytokines, for the correct inclusion in the form of the disease. The lesions seen on the CT, classified under the Balthazar score, have a prognostic value upon severity of the disease and mortality (11).

Recent treatment principles, which led to a marked decrease in the rate of mortality, rely on reducing the systemic inflamatory response, reducing the dysfunction of vital organs (sustainance of vital functions, maintaining the equilibrium of the hydro-electrolytic balance, enteral nutrition, antibiotics), ultrasound/CT - giuded precutaneous drainage of the intra-abdominal collections, postponing the surgical intervention till the moment it becomes absolutely necessary (superinfected necrotic tissue which cannot be evacuated by any other means, alarming increase of the intraabdominal pressure). Various studies from the literature underline the importance of the change of tactics used in the period of '90, when early surgical interventions were performed in favour of those performed in the later phase of the disease (26-33).The goal was to achieve a drastic reduction in the mortality rates: from 39% to 12% achieved in the study of Hartwig (34), from 56% to 27% in the study of Miller (35), from 75% to 8% (p=0.001) in the study of Basselinki (36). More often, there is a common attitude towards management of non-infected necrotic tissues, which should be treated conservatively, as any invasive manoeuvre increases the risk of suprainfection. Necrosectomy performed in this condition where the devitalised tissue margins are not clearly demarcated, can lead to major hemorrhagic complications or inclusion of viable tissue along with the necrotic ones during the maneuvre.

It is very important to identify the moment when the necrotic tissue gets superinfected, as there exists the discussion of drainage through surgical intervention (37). Clinically an alteration in the patients clinical status is seen, leucocytosis, positive hemocultures and peripancreatic gas accumulation in a CT examination. The fluid from the infected zones is sampled with the help of a fine needle (FNA) guided through CT or echoendoscopy. This method can obtain a false negative result up to 20-25% (38), but positive samples allow identification of the microorganism in 89-100% of the cases (39,40). According to some authors, antibiotic only treatment according to the antibiogram can be continued as long as the general status of the patient remains good (31,41,42).

According to the Japanese Society of Hepato-Biliary-Pancreatic Surgery (41), necrosectomy with a large drainage is a procedure to be performed in the case of suprainfected pancreatic necrotic tissue. Good results were also obtained using minimally invasive techniques like CT guided drainage of the intraabdominal collections, followed by endoscopic necrosectomy (43-46), laparoscopic necrosectomy and drainage (47), transgastric endoscopic necrosectomy (48-50), although their efficiency needs to be evaluated on a larger number of patients.

In the presence of pancreatic abcesses there is a consensus upon the necessity of the drainage (41). Sonnenberg (51) and Baril (52) had reported a success rate of 78-86% in percutaneous CT guided drainage, which was considered to be their first therapeutic option. It should be also taken into account that in the case of patients with severe form of the disease, having multiple intraabdominal collections the rate of success mentioned above decreases to 30-47% (41). In this way, whenever there are signs that the drainage is inefficient, surgical drainage will be performed.

None of the patients included in our study had received the benefit of CT-guided drainage of the collection and this represents the biggest inadequacy of the treatment that we applied. The explanation for this inadequacy can be found in the lack of experience of our service to perform such manuoevres or rendering pretty easily the imaging-guided drainage to be inefficient, whose role in postponing the surgical intervention should be taken seriously. By increasing the experience in this domain, we can certainly improve our results.

Conclusions

Acute pancreatitis represents one of the most severe abdominal pathologies, having a potential lethal evolution in a large number of cases, and with a serious consumption of human and financial resources. The results of the treatment can be improved by knowing the physiopathological phenomenon behind this pathology, early diagnosis of the form of the disease and a rapid initiation of the maintenance therapy.

Patients who need a surgical intervention will be postponed until the sepsis given by the superinfection of the necrotic zones or until abdominal compartment syndrome will appearleading todysfunction ofthe intra-abdominal organs.

Minimally invasive techniques like the imaging or endoscopic guided drainage proved themselves to be useful in gaining time and postponing the surgical moment and sometimes to be sufficient enough as therapeutic gestures.

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