RISK FACTORS FOR DEVELOPMENT OF ACUTE NECROTIZING PANCREATITIS

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FAKTORI RIZIKA ZA RAZVOJ AKUTNOG NEKROTIZUJUĆEG PANKREATITISA

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ABSTRACT

Acute necrotizing pancreatitis (ANP) is a severe form of acute pancreatitis that is associated with high morbidity and mortality. Thus, an adequate initial treatment of patients who present with acute pancreatitis (AP) based on correct interpretation of early detected laboratory and clinical abnormalities may have a significant positive impact on the disease course.

The aim of the study was to determine patient- and initial treatment- related risk factors for the development of acute necrotizing pancreatitis.

For the purpose of this study a case-control design was chosen, including adult patients treated for AP in the surgical Intensive Care Unit (sICU) of Clinical Center of Kragujevac, from January 2006 to January 2011. The cases (n=63) were patients who developed ANP, while the controls (n=63) were patients with AP without the presence of pancreatic necrosis. The controls were randomly selected from a study sample after matching with the cases by age and sex.

Significant association with the development of ANP was found for the presence of comorbidity (adjusted OR 6.614 95%CI 1.185-36.963), and the use of somatostatin (adjusted OR 7.460, 95%CI 1.162-47.833) and furosemide (adjusted OR 2710.57, 95%CI 1.996- 56.035) started immediately upon admission to the sICU.

This study suggests that comorbidities, particularly the presence of serious cardio-vascular disease, can increase the risk for development of acute necrotizing pancreatitis. The probability for the development of ANP could be reduced by the avoidance of the initial use of loop diuretics and somatostatin.

Key words: acute necrotizing pancreatitis, risk factors, comorbidity, furosemide, somatostatin

SAŽETAK

Akutni nekrotizujući pankreatitis (ANP) je teška forma akutnog pankreatisa koja je praćena visokim morbiditetom i mortalitetom. Adekvatno inicijalno lečenje pacijenata sa kliničkom slikom akutnog pankreatitisa, koje se zasniva na tačnoj interpentaciji rano dijagnostikovanih labarotorijskih i kliničkih abdormalnosti, može imati značajan pozitivan uticaj na tok bolesti.

Cilj ove studije je bio da odredi faktore rizika koji su povezani sa stanjem pacijenta i inicijalnim lečenjem na razvoj ANP.

Izabrana je „case-control" studija koja je uključila odrasle osobe koji su lečeni od akutnog pankreatitisa u hirurškoj jedinici intenzivnog lečenja Kliničkog centra Kragujevac, u periodu od januara 2006. do januara 2011. godine. Slučajevi (n=63) su pacijenti koji su razvili ANP, dok su kontrole (n=63) sa akutnim pankreatitisom bez razvoja nekroze pankreasa. Kontrole su slučajno izabrane iz studijskog uzorka nakon slaganja u polu i starosti sa slučajevima.

Značajna povezanost sa razvojem ANP je nađena za prisustvo komorbiditeta (adjusted OR 6.614 95%CI 1.185-36.963), inicijalno lečenje somatostatinom (adjusted OR 7.460, 95%CI 1.162-47.833) i furosemidom (adjusted OR 2710.57, 95%CI 1.996- 56.035) .

Rezultati ove studije ukazuju da komorbiiditet, naročito prisustvo kardiovaskularnih bolesti može povećati rizik za razvoj ANP. Verovatnoća za razvoj ANP mogla bi se smanjiti izbegavanjem inicijalne upotrebe somatostatina i diuretika Henleove petlje.

Ključne reči: akutni nekrotizujući pankreatitis, faktori rizika, komorbiditet, furosemid, somatostatin.

INTRODUCTION

Acute necrotizing pancreatitis (ANP) is an inflammatory response to functional and / or structural damage to the acini of the pancreas. It is a severe disease and is frequently associated with unfavourable outcomes. The necrosis involves pancreatic parenchyma, peripancreatic tissue or both. Approximately 5-10% of patients with acute pancreatitis develop the necrotizing form of the disease, with mortality ranging from 8% to 30%. In fact, the development of pancreatic necrosis is the most important prognostic factor that imposes a high risk of secondary infection, multiple organ failure and fatal outcome.(1.-4.)

The association with the development of acute necrotizing pancreatitis and consequent increased mortality rate has been well established for numerous factors, including older age, obesity, signs of systemic inflammatory response syndrome, increased levels of creatinine and blood urea nitrogen, hyperglycaemia, low serum calcium level, hypoalbuminaemia, high C-reactive protein level, raised lactate dehydrogenase level, and pleural effusion at admission to the hospital. (5.-7.) On the other hand, there are factors whose role in the development of the necrotizing form of AP is still controversial. These include: initial use of different modalities of enteral or parenteral nutrition, need for early and aggressive fluid replacement, the type of optimal resuscitative fluid (particularly use of various colloid solutions), and the impact of comorbidity that can be defined as the presence of one or more additional serious diseases co-occurring in patients with acute pancreatitis.(7.-8.)

The aim of this study was to investigate the association of patient- and initial treatment - related factors in patients admitted to the sICU for acute pancreatitis with the development of the necrotizing form of disease, as well as to determine their potential additive effects on the occurrence of the observed outcome.

MATERIALS AND METHODS

We have conducted a retrospective, observational, case-control study of 126 adult patients treated for AP at the surgical Intensive Care Unit (sICU) of Clinical Center of Kragujevac (CCK), Serbia, during the five-year period between January 2006 and January 2011. The main criterion for admission to sICU was haemodynamic instability that required continuous monitoring. All data were collected through review of the patients' files. The diagnosis of AP was established by the presence of abdominal pain consistent with the disease and serum amylase and / or lipase greater than three times the upper limit of normal.(1.) The presence of necrosis of the pancreatic parenchyma or the peripancreatic tissues was diagnosed by abdominal contrast-enhanced computed tomography (CECT) and is defined by the presence of nonperfusion of the pancreatic parenchyma and/or presence of local inflammatory changes with associated heterogeneous collection of both solid and liquid components.(2.) CT was performed within at least three days of admission to the sICU, and a single radiologist retrospectively interpreted the CT scans. The study protocol was approved by the Ethics Committee of CCK.

The group of cases (n=63) consisted of patients who developed ANP, and the controls (n=63) were patients with AP without the presence of pancreatic necrosis. The controls were randomly selected from a study sample after matching the cases by age and sex.

Exclusion criteria were: patients under 18 years of age, patients who developed acute pancreatitis after an operation, pregnant women, patients who were referred from the other hospitals to the sICU of the Clinical Center of Kragujevac after more than 2 days from the disease onset, and patients with incomplete data in their medical records.

The variables analysed as potential risk factors for the development of necrotizing AP included:
a) Comorbidity (including myocardial infarction, congestive heart failure, coronary artery disease, hypertensive heart disease, moderate or severe stage of chronic kidney failure, liver cirrhosis, peripheral vascular disease, cerebrovascular disease, chronic lung disease, moderate or severe liver disease, diabetes, and malignancy).
b) The levels of blood urea nitrogen, serum creatinine, blood glucose, arterial oxygen tension (PaO$_2$), partial pressure of carbon dioxide (pCO$_2$), C-reactive protein (CRP), serum protein, serum albumin, leukocyte count, heart rate, and the amount of intravenous solutions. These continuous variables were measured in the first 2 days of after admission to the sICU.
c) The presence of pleural effusion on first day of admission of a patient to the sICU, diagnosed by chest X ray.

d) Type of intravenous solution for fluid resuscitation. Colloids that were used for resuscitation were gelatin and/or hydroxyethyl starch.

e) Use of albumin 20% solution.

f) Type of nutritional support started within the first 3 days of admission to the sICU (Nutrison® solution for enteral nutritional support was used early if that could be tolerated; if not, Nutriflex® solution was used for parenteral nutrition). This variable was divided into four categories:

  1. No need for the nutrition support because regular oral feeding was resumed

  2. Total enteral nutrition,

  3. Total parenteral nutrition, and

  Combined enteral and parenteral nutrition.

g) Initial use of opioid analgesics (tramadol), somatostatin analogue octreotide, parenteral calcium preparations, and loop diuretics (furosemide).

h) Multiple Organ Dysfunction Score (MOD score) in the first 24 hours of admission to the sICU.

The differences between cases and controls in the observed numeric (continuous) variables were assessed by Student T-test for two independent samples or a Mann-Whitney U test (after estimation of data distribution using Kolmogorov-Smirnov test for normality), while for categorical variables, Chi-squared test was used. The differences were considered significant if probability of null hypothesis was less than 0.05. To estimate the association of potential risk factors and the development of necrotizing AP, crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were estimated using logistic regression analysis.

RESULTS

Baseline characteristics of the patients with and without necrotizing pancreatitis, and differences between them, are shown in Table 1. The differences between the cases and controls were significant in terms of comorbidity, presence of cardio-vascular disease, the values of the laboratory tests (CRP, blood glucose, urea, creatinine, serum protein and albumin), presence of pleural effusion and parameters of initial treatment, such as use of 20% albumin, use of opioid analgesics, use of furosemide, use of parenteral calcium preparations, type of nutritional support and type of intravenous solution used for fluid resuscitation. There were not significant differences for leukocyte count, pCO_2 value, heart rate or amount of intravenous solutions.

The results of both univariate and multivariate logistic regression analysis (Cox & Snell R square 0.450, Nagelkerke R square 0.600, Hosmer-Lemeshow Chi square 7.639, df=7, p = 0.392, overall model accuracy of 84.8%) presented in Table 2 suggest that the presence of comorbidity, as well as initial use of somatostatin and furosemide, are significantly associated with the development of necrotizing AP. For certain variables, univariate regression models in-

dicated significant influence on the development of acute necrotizing pancreatitis (see crude ORs in the Table 2). The variables contributing to development of necrotizing AP were as follows: level of C-reactive protein, presence of pleural effusion at admission to sICU, type of solution used for intravenous fluid replacement, use of opioid analgesics and nutritional support in initial treatment. The factor that was associated with protection from the development of acute necrotizing pancreatitis was the level of serum albumin at admission to the sICU. After adjustment all of these effects were lost (see adjusted OR in Table 2).

The interactions between factors that are likely to have potential additive effects on the risk of development of necrotizing AP were also examined. The analysis showed strong synergistic effects for the use of furosemide and somatostatin in initial treatment and the presence of comorbidity (Table 3).

DISCUSSION

Acute pancreatitis (AP) is an acute inflammation of the pancreas and adjacent tissue that can potentially be life threatening. There are two main clinical courses of the AP: the first is self-limited, mild form of disease, which is experienced by the majority of patients (approximately 80-85% of all cases of AP). The second form is severe pancreatitis with development of tissue necrosis and is associated with high morbidity and mortality (approximately 15–20% of patients suffer from severe, necrotizing pancreatitis). (9) Necrosis of the pancreas is a consequence of the inflammatory process and hypoperfusion due to loss of intravascular volume (marked as haemoconcentration or increasing haematocrit values). Pancreatic necrosis is an ideal place for the development of infection, which occurs in 40-70% of all patients with necrotizing pancreatitis and is the primary cause of death in the second or late phases of the disease. For these reasons, tracking a patient's progress early in the disease course and initial aggressive management have significant clinical importance. (10)

Our study showed that the presence of certain patient features (such as the presence of comorbidity), pathological laboratory findings and initial treatment were associated with development of ANP.

It ishas been shown that patients with important related comorbidities, especially with chronic cardiovascular disease, often develop necrotizing pancreatitis. This can be explained by the fact that in patients with cardiovascular disease, there is impaired perfusion of all tissues including the pancreas, which leads to the development of necrotic pancreatitis. However, in a study by Uomo et al., related comorbidity was not associated with the development of necrotizing pancreatitis. (11)

CRP is an acute phase reactant secreted by hepatocytes after stimulation by cytokines IL-1 and IL-6, and its level is increased in many inflammatory conditions. The values of CRP peak 72 hours from the onset of pain in AP,

Table 1. Baseline characteristics of the study patients

Variable	Acute pancreatitis with necrosis (cases)	Acute pancreatitis without necrosis (controls)	Test value and significance of null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Comorbidity	*Without chronic diseases* 16 (12.7%) *With any chronic diseases* 47 (37.3%)	*Without chronic diseases* 29 (23%) *With any chronic diseases* 34 (27%)	x²=5.842 p=0.016	2,506 (1.180, 5.321)
Chronic cardio-vascular disorder	Without chronic cardio-vascular disorder 26 (20,6%) With presence of chronic cardio-vascular disorder 36 (29,4%)	Without chronic cardio-vascular disorder 38 (30,2%) With presence of chronic cardio-vascular disorder 25 (19,8%)	χ^2 =6,623 p=0,036	2,285 (1.169, 4.466)
C-reactive protein (CRP) level at admission to sICU	186.47±16.32	116.78±15.89	T=-3,508 p=0,003	1.007 (1.002, 1.012)
Blood glucose level at admission to sICU	9.72±0.65	7.77±0,36	U=1462.5 Z=-2.547 p=0,011	1.140 (1.023, 1.271)
The level of blood urea nitrogen at admission to sICU	10.00±0.85	6.84±0.55	U=1343 Z=-3.013 p=0.003	1.127 (1.034,1.229)
Serum creatinine level at admission in sICU	195.82±30.171	89.90±4.33	U=1304.5 Z=-3.203 P=0.001	1.013 (1,004, 1.022)
The level of the total serum protein at admission to sICU	53.65±1.38	59.13±1.20	T=2.926 p=0,004	0.931 (0.885,0.981)
The level of the serum albumin at admission to sICU	28.41±1.15	34.07±1,12	U=559 Z=-3.874 p=0,000	0.909 (0.856, 0.965)
The presence of pleural effusion at admission	With pleural effusion 37 (29,4%) Without pleural effusion 26 (20,6%)	With pleural effusion 18 (14.3%) Without pleural effusion 45 (35,7%)	χ^2 =11,648 p=0,001	3,558 (1.697, 7.471)
Type of intravenous solution used for fluid resuscitation in initial treatment	only crystalloids 29 (23,0%) crystalloids plus colloids 34 (27,0%)	only crystalloids 45 (35,7%) crystalloids plus colloids 18 (14,3%)	χ^2 =8,383 p=0,004	2.931 (1.402, 6.129)
Type of nutritional support in initial treatment	no need for the nutritional support 18 (14,3%) total enteral nutrition 4 (3,2%) total parenteral nutrition 18 (14,3%) combined enteral and parenteral nutrition 23 (18,3%)	no need for the nutritional support 29 (23%) total enteral nutrition 3 (2,4%) total parenteral nutrition 25 (19,8%) combined enteral and parenteral nutrition 6 (4,8%)	χ^2 =13,822 p=0,003	1.535 (1.133, 2.080)
Use of albumin 20% solution in initial treatment	Yes 22 (17,5%) No 41 (32,5%)	Yes 4 (3,2%) No 59 (46,(%)	χ^2 =15,702 p=0,000	0,126 (0.041, 0.394)
Use of opioid analgesics in initial treatment	Yes, tramadol 31 (24,6%) No 32 (25,4%)	Yes, tramadol 14 (13,5%) No 46 (2635%)	χ^2 =6,596 p=0,017	2,621 (1.246, 5.516)
Use of somatostatin analogue octreotide in initial treatment	Yes 33 (26,2%) No 30 (23,8%)	Yes 17 (13,5%) No 46 (36,5%)	χ^2 =8,488 p=0,004	2,976 (1.414, 6.265)
Use of calcium in initial treatment	Yes 32 (25,4%) No 31 (24,6%)	Yes 14 (22,2%) No 49 (38,9%)	χ^2 =11,093 p=0,001	0,277 (0.128, 0.599)
Use of furosemide in initial treatment	Yes 36 (28,6%) No 27 (21,4%)	Yes 13 (10,3%) No 50 (39,7%)	χ^2 =17,666 p=0,000	5,128 (2.332, 11.280)

Table 2. Crude and adjusted odds ratios of the investigated factors potentially associated with death in patients with severe acute necrotizing pancreatitis

Risk factors	Crude OR (95% CI)	Adjusted OR (95%CI)
Comorbidity	2.506 (1.180, 5.321) *	6.614 (1.185, 36.963)*
C-reactive protein (CRP) value at admission to the sICU	1.007 (1.002, 1.012)*	1.003 (0.994, 1.112)
The value of the serum albumin at admission to the sICU	0.909 (0.856, 0.965)*	1.057 (0.941, 1.188)
The presence of pleural effusion at admission	3.558 (1.697, 7.471)*	3.399 (0.581, 19.904)
Type of solution used for intravenous fluid replacement	2.931(1.402, 6.129)*	3.041 (0.551, 16.780)
Use of furosemide in initial treatment	5.128 (2.332,11.280)*	10.57 (1.996, 56.035)*
Use of opioids analgesics (tramadol vs. no opioids analgesic was performed) in initial treatment	2,621 (1.246, 5.516)*	1.338 (0.231, 7.762)
Use of Somatostatin/Octreotide in initial treatment	2,976 (1.414, 6.265)*	7.460 (1.162, 47.833)*
Nutritional Support in initial treatment	1.535(1.133, 2.080)*	0.708 (0.292, 1.715)
Multiple Organ Dysfunction Score within the first 24 h of admission to the sICU	1.219 (0.967, 1.535)	1.009 (0.568, 1.791)

* Statistically significant association (OR)

Table 3. Interactions between the risk factors influencing development of ANP

Risk factors	Crude OR (95% CI)	Adjusted OR (95% CI)
Only comorbidity	2.506 (1.180, 5.321) *	6.614 (1.185, 36.963) *
Only use of furosemide in initial treatment	5.128 (2.332,11.280) *	10.57 (1.996, 56.035) *
Only use of somatostatin in initial treatment	2,976 (1.414, 6.265) *	7.460 (1.162, 47.833) *
Both use of furosemide and comorbidity	4.818 (2.086; 11.131) *	16.755 (2.680; 104.771)*
Both use of somatostatin and comorbidity	3.220 (1.342; 7.726) *	6.614 (1.059; 35.868) *

* Statistically significant association (OR)

and increased CRP 48 hours after admission to hospital is good predictor for development of the severe form of disease. (12) There are many studies that examined the predictive value of CRP for the development of acute necrotizing pancreatitis, and thus far, CRP has proven to be the best predictive marker. Barauskas et al. showed that patients with a CRP level below 110 mg/l have lower risk of developing necrotizing pancreatitis. (13) Cardoso et al. showed that a cut-off level of CRP that may indicate the development of necrotizing pancreatitis varied between 170 and 190 mg/l. (12) However, multiple cut-off levels have been described, and a CRP level of 150 mg/L is currently widely used as the cut-off level for development of pancreatic necrosis. (14) Our study showed that an increased level of CRP in the first 48 hours from the onset of disease is correlated with the development of pancreatic necrosis; the average CRP level of patients with pancreatic necrosis was 186 mg/l.

In severe forms of AP, pathological changes in the lung are common and are manifested as functional changes that are related to a disturbance in gas exchange, leading to the development of hypoxia and morphological changes that are manifested as pleural effusion and/or pulmonary infiltrates. For a long time, these changes have been considered significant predictive parameters, and they have been included among the Ranson, Glasgow, and APACHE II criteria. (15) Our study showed that presence of pleural effusion 24 hours after the admission was associated with

the development of necrotizing pancreatitis, which is in agreement with findings by Talamini et al. (16)

Haemoconcentration in the early course of the disease leads to stasis, thrombosis and eventually pancreatic necrosis. To prevent it, aggressive fluid resuscitation is recommended early in the course of pancreatitis, and the quantity of liquid necessary for resuscitation is 2-4 times higher (60-160 mL/kg body weight) than the needs of a healthy person.(17) Two types of fluids can be used for resuscitation, which are colloid fluids with large molecules (hetastarch, dextran 40, and albumin) and crystalloid fluids with added electrolytes (normal saline, Ringer's, and lactated Ringer's solution). Fluid resuscitation begins with intravenous crystalloid solutions, such as Ringer's lactate solution. It has been reported that lactated Ringer's solution reduced the inflammatory response in patients with acute pancreatitis in comparison to normal saline.(18) On the other hand, the combination of crystalloids and colloids (hydroxyethyl starch - HES) is also effective, increasing colloid osmotic pressure and diminishing the loss of fluid in the third space, as well as modulating the inflammatory reaction through inhibition of nuclear factor-κB activation and neutrophil adhesion and migration.(19) Our study showed that fluid resuscitation in patients with ANP was carried out with combination crystalloids plus colloids because of a high degree of haemoconcentration and a need for increased colloid osmotic pressure and decreased fluid leakage.

Acute pancreatitis is characterized by an increased metabolism and thus increasing nutritional needs. The concept of gut rest (prohibiting enteral intake) has not proved effective in the treatment of acute pancreatitis; therefore, total parenteral nutrition-TPN was initially given priority with the aim to achieve adequate nutritional needs and to prevent secretion of exocrine pancreas. However, use of TPN can increase disease severity, incidence of septic complication and hyperglycaemia. Early enteral nutrition through naso-jejunal tube maintains gut integrity, reduces translocation of bacteria from the gut, down-regulates the systemic immune response, and has many other beneficial effects, including increased production of anti-inflammatory cytokines by intestinal mucosa, especially IL-10, and increase of gastrointestinal motility.(20.-21.) Our study showed that patients with necrotizing pancreatitis received a combination of enteral and parenteral feeding due to increased metabolic needs.

Many studies have reported that hypoalbuminaemia in the early stage can lead to development of pancreatic necrosis.(22), Additionally, a lower level of plasma albumin in early stages is associated with high incidence rate of infection and variation of albumin levels is a significant risk factor for poor prognosis of patients with severe acute pancreatitis.(23) We confirmed this, because hypoalbuminaemia in the early stage of disease was associated with development of necrotizing pancreatitis, and thus, albumin solution was administered to our patients in order correct hypoalbuminaemia and to replace lost volume.

Somatostatin is a 14 amino acid peptide that acts as an inhibitor of growth hormone, as well as gastric, pancreatic, intestinal secretion, gastrointestinal motility and blood flow in splanchnic area. Octreotide is synthetic analogue of somatostatin that has a much longer half-life and causes less glucose intolerance than the native hormone.(24) The initial use of somatostatin and octreotide was justified by the traditional concept of resting the pancreas in AP. The data for use of somatostatin are controversial. Some studies reported beneficial effects of somatostatin in AP with fewer surgical complications, decrease in systemic inflammatory response (by decrease IL-6 and TNF-α level) and improvement in kidney function. (25.) Di Francesko et al. showed that administration of somatostatin induces excitation of the Sphincter of Oddi and pancreatic outflow obstruction.(26.) We show here that use of somatostatin in the early stage of disease was associated with the development of necrotizing pancreatitis.

Aggressive fluid resuscitation is very important in preventing the development of pancreatic necrosis and is performed until an adequate urinary volume is achieved. Use of diuretics before an adequate fluid resuscitation is achieved can aggravate the disease.(17) We confirmed this because patients with early use of diuretics such as furosemide more often developed necrotizing pancreatitis.

This study does have the following limitation. The influence of certain potentially confounding variables on the development of necrotic pancreatitis could not be estimated due to incomplete data records (e.g., body mass index, aetiology of acute pancreatitis, use of antibiotics in initial treatment, and type of cytokines response).

In conclusion, this study suggests that the presence of comorbidities, particularly of chronic cardiovascular diseases, is significantly associated with development of ANP. Certain laboratory findings such as high levels of CRP, low values of albumin and presence of pleural effusion could indicate which patients will develop ANP. The probability for the development of ANP could be reduced by the avoidance of the initial use of loop diuretics and somatostatin.

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COMPETING INTERESTS

The authors declare that have no conflict of interest in this study.

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