

C-reactive protein in early prediction of pancreatic necrosis

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Key words: acute pancreatitis, pancreatic necrosis, C-reactive protein.

Summary. Aim of the study – to determine relation between the C-reactive protein and pancreatic necrosis, and to estimate the prognostic value of C-reactive protein in early diagnosis of pancreatic necrosis.

Material and methods. During 2001, 78 patients with acute pancreatitis were included in the study. The clinical data, diagnostic procedures, and laboratory values were analyzed. According to severity of the disease patients were divided into two groups. Group I consisted of 17 patients with necrotic pancreatitis, group II – of 61 patients with pancreatic edema. Contrast-enhanced computed tomography scan was used to diagnose pancreatic necrosis with subsequent fine-needle aspiration for microbiological evaluation. C-reactive protein concentration in serum was measured on day 1, 2, 3, 5, 7 and 9 after admission. The sensitivity, specificity, positive and negative predictive values for different C-reactive protein concentration cut-off (100–150 mg/l) were calculated. Average C-reactive protein values were compared between groups by t test for unpaired data. The difference was assumed statistically significant when $p < 0.05$.

Results. There was no significant difference in demographic data between the groups. Necrosis of the pancreas was demonstrated on computed tomography scan in 17 cases. The highest C-reactive protein values were detected on day 3 in group I patients. The difference of average C-reactive protein concentration was significant between groups on all days except day 7. The highest sensitivity and negative predictive value (94.1% and 95.7% respectively) was obtained for C-reactive protein cut-off at 110 mg/l.

Conclusions. The results of our study show the C-reactive protein values increase significantly in early stages of necrotic pancreatitis. C-reactive protein is an important prognostic marker of pancreatic necrosis with the highest sensitivity and negative prognostic value given the cut-off is 110 mg/l. The patients with C-reactive protein below 110 mg/l are at low risk to develop pancreatic necrosis.

Introduction

The majority of patients with acute pancreatitis present with mild, uneventful course of the disease, however, in 20–25% of cases disease may take a serious course with severe local and systemic complications and there is considerable mortality. In patients with severe necrotic pancreatitis organ failure is common and may occur in the absence of infection. In the natural course of the disease, infection occurs in a considerable number of these patients. According to Atlanta definition infected pancreatic necrosis is defined as the presence of bacteria in diffuse or focal areas of intrapancreatic or extrapancreatic necrotic tissue (1). It is assumed that the most important prognostic factor of acute pancreatitis is the development of pancreatic necrosis with subsequent risk of pan-

creatic infection, multiple organ dysfunction, and death. Of patients who die of acute pancreatitis, more than 60% of deaths are due to septic complications (2). Conservative treatment of necrotizing pancreatitis is associated with favorable results. There seems to be evidence that prophylactic antimicrobial therapy may reduce the rate of pancreatic infection and thus has a positive impact on the mortality rate associated with this disease. It is important to stratify patients early for induction of antibiotic treatment (3); therefore it is very important to use some marker, which could enable to diagnose the pancreatic necrosis at the very onset of the disease (4). Ideally it should have high sensitivity and positive prognostic value, and diagnose pancreatic necrosis early (during the first 48 hours). The test should also be readily available in every clini-

cal laboratory, and it should be cheap and impersonal (5). The aim of the study was to determine the prognostic value of C-reactive protein (CRP) in early prediction of pancreatic necrosis.

Material and methods

We analyzed case records of the patients with acute pancreatitis, managed during the period of 2001–2002 at the Department of Surgery, Kaunas University of Medicine Hospital. Acute pancreatitis was diagnosed according to the clinical symptoms and elevation of serum α -amylase more than three times. CRP was measured every day for 5 consecutive days as well as on day 7 and day 9 after admission. When CRP value exceeded 120 mg/l or clinical picture of severe acute pancreatitis was present, the contrast-enhanced computed tomography (CT) scan was performed. All the data was included into the database created for this study. The patients were divided into two groups: group I – patients with necrotic pancreatitis (NP), group II – patients with mild pancreatitis (pancreatic edema – PE). The patients were included into group I after demonstration of pancreatic necrosis on CT scan or at surgery. Fine needle aspiration (FNA) was practiced in patients with pancreatic necrosis and when infection was demonstrated, surgical drainage of infected pancreatic necrosis was performed. Patients with sterile pancreatic necrosis had no surgery. Student's *t* test for independent data was used to compare concentrations of CRP between groups. Sensitivity (S), specificity (SP), positive prognostic value (PPV), and negative prognostic value (NPV) for CRP cut-off concentrations from 100 to 150 mg/l were calculated to clarify the best cut-off concentration for prognosis of pancreatic necrosis.

Results

Seventy-eight patients were treated because of acute pancreatitis from January 2001 to January 2002.

None of the patients had attacks of acute pancreatitis previously. There were 17 (21.8%) patients with NP and 61 (78.2%) patients with PE (Table 1). The average age of patients in both groups was similar. Men predominated in both groups, but the difference was negligible in the NP group (52.9 vs. 47.8). Gallstones and alcohol were shown to have induced mild pancreatitis in 24.6% and 29.6% of cases respectively. Etiologic factor for necrotic pancreatitis in 52.9% of patients was gallstones. Evident causative factor was not revealed in one third of patients in both groups.

The contrast-enhanced CT scan was performed in 27 cases, so all patients with pancreatic necrosis were examined, some of them repeatedly. Low volume necrosis (<30%) was present in 10 (58.8%), 30–50% necrosis – in 2 (11.8%), and subtotal necrosis (>50%) – in 5 (29.4%) cases. The patients with necrosis of the pancreas compounded 63% of those who underwent CT scan. Six patients with pancreatic necrosis underwent surgery: three of them on the first day of hospitalization because of the signs of peritonitis and uncertain diagnosis, suggestive of viscus perforation, and 3 – in the later course of the disease after FNA demonstrated pancreatic and/or peripancreatic necrosis.

The average concentrations of CRP in both groups are shown in the Figure. Mean values of CRP differed in the groups significantly from the day of hospitalization except for day 7 (Table 2).

Sensitivity, specificity, positive, and negative predictive values for various CRP cut-off concentrations were determined (Table 3). With CRP cut-off value of 100 and 110 mg/l all the parameters were equal. Increasing CRP cut-off values resulted in significant decrease of sensitivity and negative predictive value, whereas only slight increase of specificity and positive predictive value was demonstrated.

Table 1. The characteristic of the patients in groups

Feature	Group I (necrotic pancreatitis)	Group II (edemic pancreatitis)
Case number (n)	17	61
Male	9 (52.9 %)	37 (60.7 %)
Female	8 (47.8 %)	24 (39.3 %)
Average age (years)	55.6	49.1
Etiology:		
alcohol	17.6 %	29.6 %
gallstones	52.9 %	24.6 %
other	29.4 %	36 %

Table 2. Comparison of average CRP values between groups (necrotic pancreatitis vs pancreatic edema)

Number of days from beginning of disease	Average CRP mg/l		95 % CI	P value
	NP	PE		
1	159.8	33.9	29.4–222.3	0.014
2	162.8	39.3	39.2–207.7	0.008
3	377.7	139.1	118.4–358.1	0.001
5	283.4	107.7	69.0–282.5	0.005
7	199.0	104.0	–101.3–291.1	0.3
9	180.8	57.0	28.8–278.8	0.017

NP – nekrotic pancreatitis, PE – pancreatic edema, CRP – C-reactive protein.

Table 3. Sensitivity, specificity, positive and negative prognostic values for various CRP cut-off concentrations

CRB koncentracija (mg/l)	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)
100	94.1	64.7	57.1	95.7
110	94.1	64.7	57.1	95.7
120	88.2	64.7	55.6	91.7
130	82.4	67.6	56	88.5
140	76.5	76.5	61.9	86.7
150	70.6	76.5	60	83.9

CRP – C-reactive protein, PV – prognostic value.

Discussion

The concept of conservative management of necrotizing pancreatitis originates from our understanding of two-phase pattern in the natural course of the disease. The first two weeks are characterized by a systemic inflammatory response syndrome, which is maintained by release of inflammatory mediators (6). Secondary pancreatic infection develops usually in the second phase of the disease, leading to multiple organ failure with a twelve-fold increase in mortality rate (4). As infection of the necrotic pancreas has been considered a secondary phenomenon it should be at least theoretically preventable by proper antibiotic therapy. Early diagnosis of pancreatic necrosis is extremely important, as it is obvious that a beneficial effect of antibiotic treatment is limited to patients with acute necrotizing pancreatitis (7). There is data showing that pancreatic necrosis develops during the first 48–72 hours from the onset of acute pancreatitis (8). Markers for necrosis are looked for among the substances that reach their peak concentrations in serum or urine during the first 24–48 hours. The most often explored are CRP, granulocyte elastase (9), tumor

necrosis factor (TNF) (10), interleukin 6 (6), α_1 -antitrypsin (11), trypsinogen (12), pancreatic ribonuclease (13), trypsinogen activating peptide (TAP) (14), carboxypeptidase B activating peptide (CAPAP) (15), human pancreas-specific protein/procarboxypeptidase B (hPASP/PCPB) (16), and serum amyloid A (17, 18). While CRP is readily available in all clinical laboratories, all other discussed parameters are not. Their use is still within the limits of clinical studies. The clinical use of these tests in the present form is limited due to drawbacks in terms of test performance and cost factors.

The CRP is non-specific mediator of inflammation, produced in hepatocytes. Its production and excretion is stimulated by interleukin 1 and 6. The CRP is considered to be quite a late indicator of pancreatic necrosis with peak concentrations in blood serum detected after 72 hours (19). Similarly our results revealed the highest average CRP concentration in the group of patients with necrotizing pancreatitis on the third day after admission. It should be mentioned that already on the first day of the disease average concentration of CRP differed statisti-

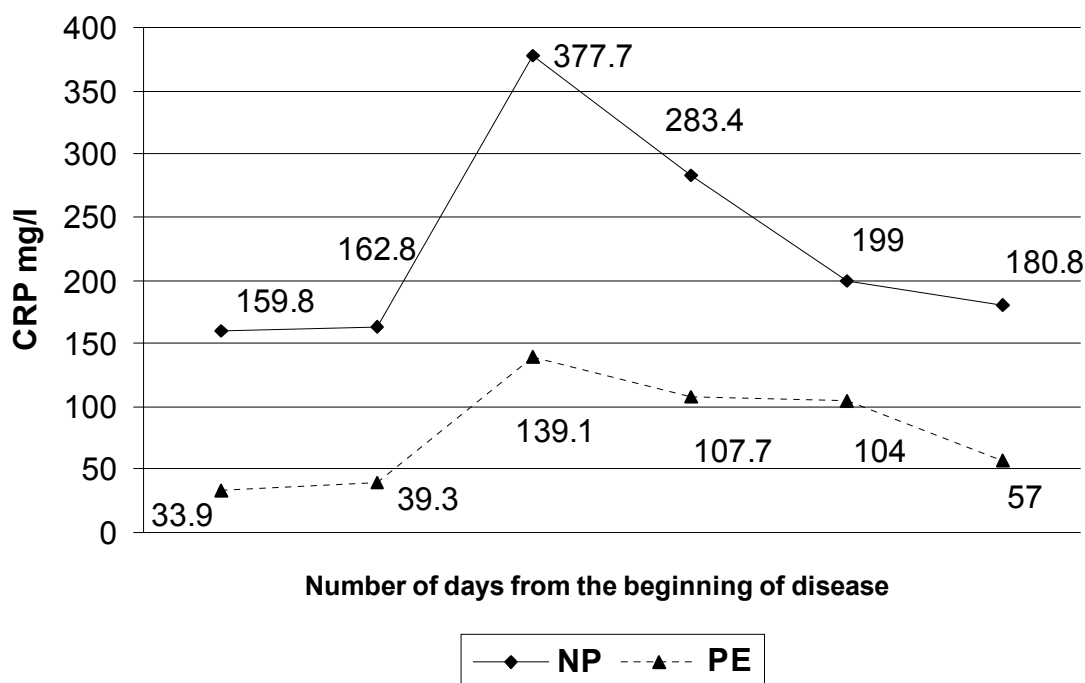


Fig. The range of mean CRP concentration in the groups

cally significantly between the groups of edematous and necrotic pancreatitis. The only explanation for this phenomenon might be delayed admission of patients with acute pancreatitis. Anyway this enabled us to use CRP as the early marker of pancreatic necrosis, having high sensitivity and negative prognostic value. As some patients are not hospitalized on the first day of the disease, it is very important that elevated CRP remains long enough in the course of the disease. On the day seven the difference of average CRP between groups was not statistically significant. Possible explanation might be too small number of CRP tests performed in the PE group, but anyway, the trend of increased CRP concentrations in NP group is obvious. Similar persistence of elevated CRP values up to 14-16 days was reported by M. Buechler et al (20).

After years of discussion there is still no consensus of the cut-off value for CRP test. Quite a wide range of CRP cut-off values between 120 and 210 mg/l have been discussed by various authors (21, 22). The lower the chosen cut-off, the higher is sensitivity and negative prognostic value of the test. On the other hand the higher cut-off values are associated with increasing specificity and positive prognostic value.

It must be determined what is more important in clinical setting – to attribute patients with edematous pancreatitis to the group of necrotic pancreatitis or

vice versa. The chosen cut-off should let us diagnose pancreatic necrosis with the highest accuracy, paying no much attention to false positive result. Hyperdiagnosis of pancreatic necrosis will result in an early treatment with antibiotics in a subset of patients who really do not have necrosis of the pancreas. This would match the CRP cut-off at 110 mg/l according to our data, showing the highest sensitivity and negative prognostic value, 94.1% and 95.7% respectively. There is no doubt that in patients with edematous pancreatitis infectious complications are rare. Administration of antibiotics will not have any positive impact on the patient's course. With regard to the development of bacterial resistance, it might be even harmful. Although with certain drawbacks, the latter approach ensures all the patients with existing pancreatic necrosis will receive beneficial treatment with antibiotics (7).

The CRP test with its diagnostic characteristics is far from ideal test for detection of pancreatic necrosis. According to our results, the CRP cut-off at 110 mg/l makes it possible to determine the group of patients with the lowest risk of pancreatic necrosis with almost 96% overall accuracy. The latter group will need neither antimicrobial therapy nor CT scan. Thus the contrast-enhanced abdominal CT scan, the most informative imaging technique up to date is reserved to the cohort of high-risk patients to develop pancreatic necrosis (23).

Conclusions

The results of our study show that the CRP values increase significantly in early stages of necrotic pancreatitis. It is an important prognostic marker of pan-

creatic necrosis with the highest sensitivity and negative prognostic value given the cut-off is at 110 mg/l. The patients with CRP values below 110 mg/l are at low risk to develop pancreatic necrosis.

C reaktyviojo baltymo reikšmė ankstyvajai kasos nekrozės diagnostikai

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Raktažodžiai: C reaktyvusis baltymas, kasos nekrozė, ūminis pankreatitas.

Santrauka. Darbo tikslas. Nustatyti C reaktyviojo baltymo koncentracijos priklausomumą nuo kasos nekrozės ir nustatyti šio baltymo prognostinę reikšmę ankstyvajai kasos nekrozės diagnostikai.

Tyrimo medžiaga ir metodai. Atlikome Kauno medicinos universiteto klinikų Chirurgijos skyriuje ligonių, gydytų 2001 metais dėl ūminio pankreatito, ligos istorijų analizę. Ligonius suskirstėme į dvi grupes: pirmąją grupę sudarė 17 ligonių, sirgusių ūminiu nekrozinu pankreatitu; antrąją – 61 ligonis, kuriam buvo diagnozuotas ūminis edeminis pankreatitas. Analizavome klinikinius, diagnostinių ir laboratorinių tyrimų duomenis. Kasos nekrozei diagnozuoti naudojome pilvo organų kompiuterinę tomografiją su intraveniniu kontrastiniu tirpalu. Nustačius kasos nekrozę, atliktos nekrozinio audinio punkcijos (plona adata) ir mikrobiologinis punktato įvertinimas. C reaktyviojo baltymo koncentracija kraujo serume buvo tiriama 1, 2, 3, 5, 7 ir 9 gydymo stacionare parą. Apskaičiuotas pastarojo tyrimo jautrumas, specifiskumas, teigiama ir neigiama prognostinė vertė parinkus įvairias (nuo 100 iki 150 mg/l) C reaktyviojo baltymo koncentracijos ribas. Šio baltymo koncentracijos vidurkiams grupėse palyginti naudotas t testas neporinėms imtims. Skirtumas laikytas statistiškai reikšmingas, kai $p < 0,05$.

Rezultatai. Demografiniai rodikliai abiejų tiriamųjų grupių buvo panašūs. Kasos nekrozė, atlikus pilvo organų kompiuterinę tomografiją, nustatyta 17 ligonių. Aukščiausios C reaktyviojo baltymo reikšmės nustatytos trečiąją gydymo stacionare parą. Statistiškai reikšmingi C reaktyviojo baltymo koncentracijų vidurkių skirtumai grupėse buvo 1–5 ir 9 dienomis. Aukščiausias jautrumas ir neigiama prognostinė C reaktyviojo baltymo reikšmė (94,1 ir 95,7 proc., atitinkamai), nustatyti parinkus 110 mg/l koncentracijos ribą.

Išvados. Šio tyrimo duomenimis, ligonių, sergančių ūminiu nekrozinu pankreatitu, C reaktyviojo baltymo koncentracija būna žymiai didesnė. Tai yra svarbus ir paprastai nustatomas ankstyvasis kasos nekrozės žymuo. Parinkus 110 mg/l C reaktyviojo baltymo koncentracijos ribą, tyrimas pasižymi dideliu jautrumu bei neigiama prognostine verte. Ligoniams, kuriems C reaktyviojo baltymo koncentracija ligos eigoje neviršija 110 mg/l, yra minimali kasos nekrozės rizika.

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Received 10 January 2003, accepted 20 September 2003