

Procalcitonin is an effective tool for the diagnosis of generalized forms of infectious complications in patients with acute necrotizing pancreatitis

Prokalcytonina jako skuteczne narzędzie w diagnostyce uogólnionych powikłań infekcyjnych u pacjentów z ostrym martwiczym zapaleniem trzustki

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Słowa kluczowe: ostre zapalenie trzustki, prokalcytonina, powikłania infekcyjne.

Abstract

Introduction: Purulent complications worsen the prognosis in patients with acute necrotizing pancreatitis (ANP). Recently procalcitonin (PCT) was proposed as a diagnostic criterion of bacterial contamination of pancreatic necrotic tissue.

Aim of the research: To evaluate the efficacy of PCT for the early diagnosis of infectious complications of ANP.

Material and methods: We performed a prospective cohort study of 151 patients with ANP. Before interventional treatment, plasma samples were collected for PCT determination. According to microbiological assay, they were categorized into 4 groups: SIRS without infection, local infection, and sepsis and septic shock. The utility of PCT for diagnosis of infectious complications of ANP was determined by ROC-analysis.

Results: Infected ANP was diagnosed in 89 (55.6%) patients. Local purulent complications were established at 27 cases, sepsis in 33, and septic shock in 29 patients. In 62 patients with sterile ANP the PCT concentration was higher than in healthy individuals and reached 1.34 ± 0.19 ng/ml ($p = 0.045$). The development of infected ANP was accompanied by an increase of PCT concentration in patients with sepsis to 5.03 ± 1.38 ng/ml ($p = 0.001$) and septic shock – up to 7.21 ± 1.91 ng/ml ($p = 0.001$), while in persons with localized form it was 2.03 ± 0.48 ng/ml ($p = 0.072$). Procalcitonin level above 4.0 ng/ml was prognostically unfavourable for the survival of patients.

Conclusions: Serum PCT level is an effective tool for the diagnosis of generalized infectious complications of ANP. Its level over 4.0 ng/ml indicates an unfavourable prognosis for patients' survival.

Streszczenie

Wprowadzenie: Powikłania ropne pogarszają rokowanie u pacjentów z ostrym martwiczym zapaleniem trzustki (*acute necrotizing pancreatitis* – ANP). Ostatnio pojawiły się doniesienia wskazujące, że stężenie prokalcytoniny (PCT) może stanowić kryterium diagnostyczne zakażenia bakteryjnego w tkance martwiczej trzustki.

Cel pracy: Ocena przydatności oznaczenia PCT we wczesnej diagnostyce powikłań infekcyjnych ANP.

Materiał i metody: Przeprowadzono prospektywne badanie kohortowe z udziałem 151 pacjentów z ANP. Przed podjęciem leczenia interwencyjnego od pacjentów pobrano próbki osocza w celu oznaczenia PCT. Na podstawie wyników badań mikrobiologicznych podzielono je na 4 grupy: SIRS bez zakażenia, zakażenie miejscowe, sepsa i wstrząs septyczny. Użyteczność oznaczenia PCT w diagnostyce powikłań infekcyjnych ANP określono za pomocą analizy ROC.

Wyniki: Zakażenie w przebiegu ostrego zapalenia trzustki rozpoznano u 89 (55,6%) pacjentów. Miejscowe powikłania ropne stwierdzono w 27 przypadkach, sepsę u 33, a wstrząs septyczny u 29 chorych. U 62 pacjentów z jałowym ANP stężenie PCT było wyższe niż u osób zdrowych i wynosiło $1,34 \pm 0,19$ ng/ml ($p = 0,045$). Rozwojowi zakażenia w przebiegu ANP towarzyszył wzrost stężenia PCT u chorych z sepsą do $5,03 \pm 1,38$ ng/ml ($p = 0,001$) i wstrząsem septycznym – do $7,21 \pm 1,91$ ng/ml ($p = 0,001$). U osób z zakażeniem miejscowym stężenie wynosiło $2,03 \pm 0,48$ ng/ml ($p = 0,072$). Stężenie PCT powyżej 4,0 ng/ml było rokowniczo niekorzystne dla przeżycia pacjentów.

Wnioski: Oznaczanie stężenia PCT w surowicy jest skutecznym narzędziem w diagnostyce uogólnionych powikłań infekcyjnych ANP. Stężenie PCT powyżej 4,0 ng/ml wskazuje na niekorzystne rokowanie co do przeżycia pacjentów.

Introduction

Acute pancreatitis is one of the most severe and dangerous diseases of the abdominal organs [1]. Despite the progress achieved in recent decades in conservative and surgical treatment, lethal outcomes with acute necrotic pancreatitis (ANP) remain high – from 9% to 36% [2]. There is no doubt that the high lethal outcome with purulent-septic complications in the majority of cases is caused by late diagnostics, which is of principal value in choosing therapeutic tactics. At the same time, clinical and laboratory parameters of the systemic inflammatory response syndrome (SIRS) are nonspecific and insensitive to sepsis, and gas available inside pancreatic necrosis found by means of computed tomography (CT) in certain cases is indicative of its connection with the digestive tract [3, 4]. In recent years, to make differential diagnostics between systemic inflammatory response and sepsis, various serological inflammatory markers have been used, including procalcitonin (PCT) [5, 6].

Aim of the research

Purpose of our research was to evaluate the utility of PCT for the early diagnosis of infectious complications of ANP.

Material and methods

This prospective observational cohort study was performed at Regional Emergency Hospital, Chernivtsi, Ukraine, between February 2016 and December 2020. The study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics review board of the Regional Emergency Hospital approved the study. Patients or their legal representatives gave written informed consent. During this period 758 patients with acute pancreatitis were admitted to the clinic. Patients were included in the current prospective study if they fulfilled the inclusion criteria of signs of pancreatic necrosis on contrast-enhanced computed tomography. Necrosis was diagnosed by lack of pancreas enhancement on contrast computed tomography, which was a sign of impaired or absent tissue perfusion. There were 211 cases of ANP. Patients were not enrolled to the study if any of the following criteria were present: a) age < 18 and > 80 years; b) recent surgical interventions; c) psychoses; d) pregnancy; and e) previously history of chronic pancreatitis. After exclusion of the above-mentioned cases, we enrolled 151 patients with ANP in the current study. All of them were admitted to a single intensive care department.

Severity of ANP was determined according to the recently revised Atlanta classification [7] by presence and duration of organ failure (OF) as well as by APACHE II score and SIRS criteria. OF for respiratory, cardiovascular, and renal system was defined by mod-

ified Marshall scoring system. Neurological dysfunction was established by Glasgow coma score, hepatic by Child-Pugh classification [8], and gut failure according to acute gastrointestinal injury score [9].

In line with international guidelines, intervention was generally only performed in cases of suspected or confirmed infection of pancreatic necrosis or peripancreatic necrosis alone. The decision to intervene was mostly based on clinical grounds (i.e. deterioration). Whenever possible, intervention was postponed until approximately 4 weeks after the onset of disease. Microbiological investigations of biological material from necrotic collections as well as blood culture were performed at intervention, and every day if draining was performed until removal of the drain. Only cases with positive bacterial growth were recognized as infected ANP. To establish the utility of PCT for the diagnosis of infectious complications of ANP, its concentration was determined before performing any invasive procedure (punction, drainage, surgery) by collection of EDTA plasma samples. Additional plasma samples were obtained in cases with confirmed infection every 72 h until normalization of the patient's condition and were used for determination of utility of PCT level for prognosis of the patient's survival. The plasma samples were categorized into groups according to the patient's conditions (SIRS without infection, local infection, sepsis and septic shock). The diagnoses of SIRS, sepsis, and septic shock were made according to the criteria described by the American College of Chest Physicians/Society of Critical Care Medicine [10]. Plasma samples for the reference level of PCT were obtained from generally healthy patients who were operated for elective surgical pathology (uncomplicated inguinal hernia). The plasma samples were stored at -70°C until measurement. PCT concentration in plasma samples was measured by immunofluorescence analysis kit ("Vector-Best", Russian Federation).

Statistical analysis

Results of PCT determination were summarized by calculating mean values and their respective standard errors of the mean (SEM). Two-group comparisons were performed using the Mann-Whitney *U*-test with the Bonferroni correction, and multiple comparisons were performed using the Kruskal-Wallis *H* test or one-way repeated-measures analysis of variance (ANOVA) with Dunnett's multiple comparison tests. We used the cut-off value obtained by receiver-operating characteristic (ROC) analysis. Values of *p* less than 0.05 were considered to indicate statistical significance. Group comparisons and ROC analyses were performed using JMP software (SAS Institute, Cary, North Carolina, USA). Analyses of Spearman correlation coefficients and interactions were performed using SPSS 18 software (SPSS, Chicago, Illinois, USA).

Table 1. Procalcitonin level, APACHE II score, organ failure, and mortality in patients with ANP

Groups	Procalcitonin [ng/ml]	APACHE II, score	Transient/persistent OF, n	Mortality, n (%)
Healthy (n = 10)	0.27 ±0.07	0	0	0
ANP without infection (n = 62)	1.34 ±0.13	4 ±1	11/7	7 (11.3)
Local infection (n = 27)	2.03 ±0.48	6 ±0.7	17/0	0
Sepsis (n = 33)	5.03 ±1.38*	12 ±1*	0/33	6 (18)
Septic shock (n = 29)	7.21 ±1.91*	23 ±2*	0/29	18 (62)
Survived (n = 120)	4.93 ±0.56	13 ±1	59/16	–
Deceased (n = 31)	8.44 ±0.76 [‡]	24 ±2 [‡]	0/31	–

**P* < 0.05 in comparison with healthy persons; [‡]*p* < 0.05 in comparison with ANP patients without infection; OF – organ failure.

Results

According to recommendations of the working group on acute pancreatitis classification (Atlanta, 2012), the severity of ANP in 101 patients with transient OF was assessed as moderate, and in 50 patients with permanent OF – as severe. Necessity for interventional treatment occurred in 74 patients with acute necrotic collections in terms before the 4th week since the onset of disease. Positive bacterial growth was found in 41 (55.4%) of them. During the post-operative period new cases of OF were diagnosed in 12 (16.2%) patients, and in 16 (21.6%) cases multiple OF occurred. Secondary infection of necrotic collections was detected in 43 (58.1%) of the operated patients; in 10 (13.5%) cases signs of generalization and development of sepsis were found. After the 4th week since onset of the disease interventional treatment was applied in 41 (53.2%) patients with walled-off pancreatic necrosis. Secondary infection of necrotic collections was found in 6 (14.6%) cases, new cases of OF in 5 (12.2%), and development of multiple OF in 3 (7.3%). Altogether, infected ANP was confirmed by bacteriological examination in 89 (58.9%) out of 151 patients with SIRS signs, including local purulent complications in 27 case, sepsis in 33, and septic shock in 29. There were 62 patients with sterile ANP manifested with SIRS (Table 1).

In patients with SIRS without infection the PCT concentration was on average 1.34 ±0.19 ng/ml and did not increase significantly (*p* > 0.05) compared to the parameters of healthy individuals. The PCT level in the majority of patients with sterile ANP was within the limits 0.37–0.67 ng/ml. It increased to 1.28 ±0.32 ng/ml in persons with subtotal necrosis of pancreas (> 50%) and to 1.54 ±0.12 ng/ml in 10 patients admitted in the condition of pancreatogenic shock.

Development of infected ANP was associated with an increase of PCT concentration on an average 4.35 ±0.76 ng/ml, which appeared to be 3–4 times higher

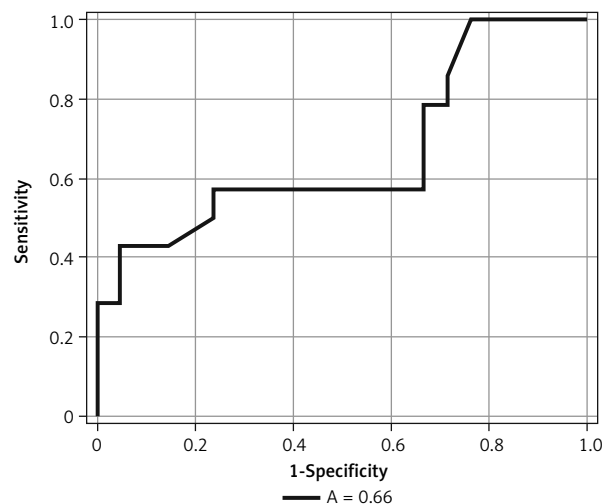


Figure 1. ROC curves for diagnosis of local infectious complications by procalcitonin in patients with acute necrotizing pancreatitis

than the parameters of patients with SIRS without infectious complications (sterile ANP). At the same time, changes of PCT concentration became significant only in the case of generalization of infectious complications: in patients with sepsis it reached 5.03 ±1.38 ng/ml (*p* = 0.001) and with septic shock – 7.21 ±1.91 ng/ml (*p* = 0.001), while in persons with localized form it was 2.03 ±0.48 ng/ml (*p* = 0.072).

Roc-analysis confirmed difference of PCT diagnostic efficacy in these 2 subgroups of patients (Figures 1 and 2). In patients with local infectious complications AUC ROC was 0.665 ±0.10 (*p* = 0.102), while in persons with generalization (sepsis and septic shock subgroups) it reached 0.796 ±0.06 (*p* = 0.0002).

The overall mortality was 11.3%. In deceased individuals the PCT level reached 8.44 ±0.76 ng/ml (*p* = 0.0001). In surviving patients with infected ANP the values of PCT before surgery remained at the same level usually after 2–4 days. It returned to the

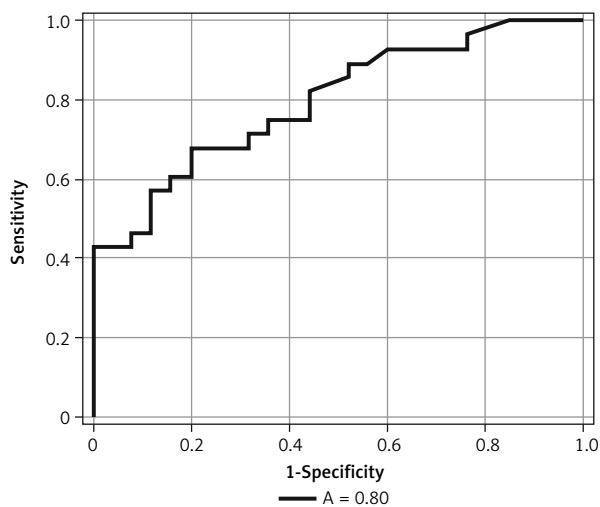


Figure 2. ROC curves for diagnosis of generalized infectious complications by procalcitonin in patients with acute necrotizing pancreatitis

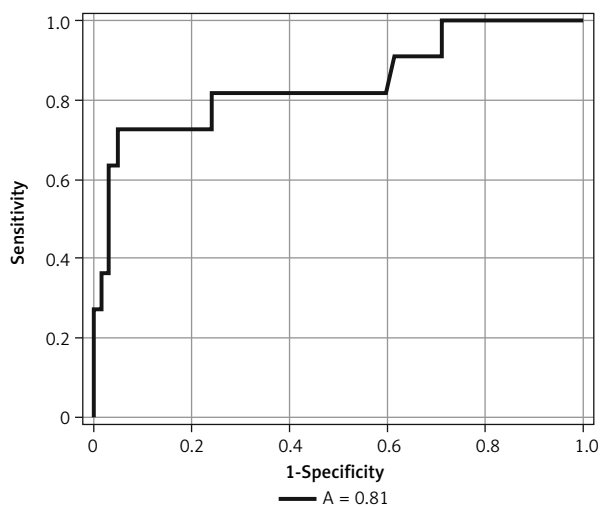


Figure 3. ROC curves for mortality prognosis by procalcitonin in patients with acute necrotizing pancreatitis

normal values on the 6th–8th day. Correlation between the PCT level and severity of the patient's condition according to APACHE II score reached $r = 0.688$, $p = 0.001$. According to ROC analysis, a PCT level over 4.0 ng/ml within 6 days of the postoperative period was associated with an unfavourable prognosis for patient survival (Figure 3).

Discussion

According to literature data, PCT together with interleukin-6 concentration could increase in patients with heat shock as well as in certain haematological patients by “non-septic way” [11]. Patients with sterile ANC operated on up to the 4th week did not develop increased PCT concentrations above 2.05 ng/ml,

even in the case of major surgery being performed. Contrary to the hormone calcitonin synthesized by the parafollicular C-cells of the thyroid gland, PCT is synthesized mainly in response to infectious inflammatory processes in different organs (liver, lungs, kidneys, muscles) [12] and enters the blood circulation. The main stimulators of PCT entering the blood are bacteria and their endotoxins as well as pro-inflammatory cytokines [13]. In comparison with the parameters of sterile ANP, patients with only local purulent complications developed inconsiderable PCT increase on average up to 2.03 ± 0.48 ng/ml ($p > 0.05$). ROC analysis showed that the efficacy of PCT for the diagnosis of such infectious complications was low: AUC ROC reached 0.665 ± 0.101 only. PCT levels from 0.5 to 2.0 µg/ml are situated within the so-called “grey area” [14], and such values require repeated determination. At the same time, in the majority of such patients, moderate ANP was diagnosed and persistent OF occurred in 17 observations. In patients with sepsis the concentration of PCT increased to 5.03 ± 1.38 ng/ml ($p = 0.001$) and in septic shock observations, up to 7.21 ± 1.91 ng/ml ($p = 0.001$). AUC ROC for PCT in sepsis cases reached 0.802 ± 0.048 (95% CI: 0.745–0.935, $p < 0.0001$), which enables the diagnosis of the infectious character of SIRS in them with high sensitivity and specificity. According to ROC analysis the cut-off level of PCT for infectious complications diagnosis was 1.8 ng/ml (sensitivity – 75.1%, specificity – 71.4%).

Also, the degree of PCT increase in the blood plasma correlated with the severity of the patients' condition (Table 1). Thus, in 11 out of 33 patients with sepsis, persistent OF developed, and in 6 of them – multiple OF. Persistent OF was diagnosed in all 29 patients with septic shock, and multiple OF in 19 of them. In deceased individuals the PCT level was twice as much as in the surviving patients ($p < 0.05$). A significant correlation between PCT level and severity of the patient's condition according to APACHE II score was found; its level over 4.0 ng/ml was associated with a negative prognosis for patient survival.

Conclusions

Serum procalcitonin level is an effective tool for the diagnosis of generalized purulent-septic complications in patients with acute necrotic pancreatitis, with a cut-off value over than 1.8 ng/ml (sensitivity – 75.1%, specificity – 71.4%).

The degree of increase of the serum procalcitonin concentration correlates to the severity of the patient's condition according to APACHE II score. Its level over than 4.0 ng/ml indicates an unfavourable prognosis for patient survival.

Conflict of interest

The authors declare no conflict of interest.

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