

Procalcitonin is a predictive marker for severe acute pancreatitis

Prokalsitonin şiddetli akut pankreatitin bir belirteçidir

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BACKGROUND

Early identification of patients who develop severe acute pancreatitis and those who can benefit from intensive care is important. We studied whether procalcitonin, a marker of systemic inflammation, is important in the differential diagnosis of patients with mild and severe acute pancreatitis.

METHODS

Patients were divided into two groups (mild and severe form) prospectively. Procalcitonin levels and the Ranson's and Acute Physiology and Chronic Health Evaluation II scores were determined both at admission and during the follow-up.

RESULTS

Of the 65 patients with acute pancreatitis, 46 had mild and 19 had severe pancreatitis. Sensitivity and specificity values for patients calculated using procalcitonin level at 0.5 ng/ml, Ranson's score at 3 and APACHE II score at 8 cut-off levels, were 100%, 84% and 89%; and 84%, 63% and 89% respectively.

CONCLUSION

Procalcitonin is a practical, simple parameter that can be used in order to diagnose severe acute pancreatitis earlier and to monitor the clinical prognosis of the disease.

Key Words: APACHE II; pancreatitis/blood/diagnosis; procalcitonin; prognosis.

AMAÇ

Sistemik komplikasyonları ile karakterize şiddetli akut pankreatitin tedavi planlanmasında hastalığın erken tehis ve yoğun bakım ihtiyacının belirlenmesi önemlidir. Bu çalışmada, sistemik enflamasyon belirleyicisi prokalsitoninin ödematöz ve şiddetli akut pankreatit ayırıcı tanısındaki yeri tartışıldı.

GEREÇ VE YÖNTEM

Prospektif olarak akut pankreatitli hastalar ödematöz ve şiddetli form olarak iki gruba ayrıldı. Ranson ve APACHE II skorları ve prokalsitonin seviyeleri başvuruda ve takipte karşılaştırıldı.

BULGULAR

Akut pankreatit tanısı alan toplam 65 hastanın 46'sı ödematöz 19'u şiddetli form idi. Prokalsitonin 0.5 ng/dl, Ranson skoru 3 ve APACHE II skoru 8 cut-off seviyelerinde duyarlılık ve özgüllükleri sırasıyla %100, %84, %89 ve %84, %63, %89 idi.

SONUÇ

Prokalsitonin, şiddetli akut pankreatitin erken tanısı ve klinik prognozunun takibinde kullanılabilen basit ve pratik bir belirteçtir.

Anahtar Sözcükler: APACHE II; pankreatit/kan/tanı; prokalsitonin; prognoz.

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Early diagnosis of severe acute pancreatitis is important for the timely initiation of intensive support treatment, identifying complications as soon as possible and for the transferring of patients to specialized centers. The severity of acute pancreatitis can not always be reliably identified by clinical approaches at the time of admission to hospital.^[1] Various biochemical parameters, computerized tomography and certain scoring systems are used for this purpose and to determine the need for intensive care. The Ranson and Acute Physiology And Chronic Health Evaluation (APACHE) II scoring systems are frequently used to identify the severity of pancreatitis, but they are not practical because they require a number of parameter measurements to be concluded during scoring.^[2-4] For early prognosis in acute pancreatitis patients, various markers such as α 1-antitrypsin, urinary trypsinogen activating peptide, amyloid A and C-reactive protein (CRP) have been determined. Of these, only CRP is clinically used. However, CRP reaches its peak level only after 72 h following the emergence of the symptoms. At the time of admission to hospital, the sensitivity of CRP is 47%, similar to that of clinical examination.^[5-9] The measure that should be used in differentiation of severe pancreatitis and determining prognosis should be simple and cheap and should have a high rate of accuracy. As yet, no such a method reached this ideal.

Procalcitonin is a calcitonin propeptide (molecular mass 13 kDa) made up of 116 amino acids. It is reported to increase early in severe infection and inflammation; values above 0.5 ng/ml are considered abnormal.^[10,11] In this study we investigated the validity of procalcitonin as a biochemical marker in the early diagnosis of acute pancreatitis and for monitoring prognosis in mild and severe cases.

MATERIALS AND METHODS

Patients who were diagnosed as having acute pancreatitis at first admission to the Firat University Faculty of Medicine General Surgery Clinic between February 2001 and April 2004 were included in the study irrespective of etiology. Patients duration of symptoms was less than 48 hours. Pancreatitis attacks were classified as severe or mild according to the Atlanta International Symposium criteria.^[12] Mild attacks were defined as those with minimal organ dysfunction and

recovery without problems, while severe attacks were those with organ failure as well as systemic and local complications. Patients with severe pancreatitis were confirmed by computerized tomography, lavage, surgical exploration, clinical prognosis and/or post-mortem examination.

Ranson's at 48th hour and APACHE II at the day of admission scoring of patients were performed. Blood samples were taken on admission when the patients were referred to the clinic and on succeeding days. Samples were stored at -20°C. Procalcitonin values were measured by an immunoluminometric method using the LUMI test-PCT-kit (B.R.A.H.M.S. Diagnostica GmbH, Berlin, Germany). The analytic assay sensitivity is approximately 0.1 ng/ml. The functional assay sensitivity (20% inter-assay variation coefficient) is approximately 0.3 ng/ml. We obtained approval from local research ethics committee.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 10.0 (SPSS, Chicago, Illinois, USA). The Mann-Whitney U-test and Fisher's exact test were employed for comparisons between groups, and values $p < 0.05$ were considered significant. Repeated measurements variance analysis (repeated measures ANOVA) was applied to procalcitonin values in both the mild and severe pancreatitis groups, measured in the first six days; $p < 0.05$ was taken as the criterion of statistical significance.

RESULTS

Of the 65 patients diagnosed as having acute pancreatitis, 32 (49%) were male and 33 (51%) were female. The mean age of the patients was 55.3 (23-85) years. The etiology was biliary in 46 cases (71%) while the remaining 19 pancreatitis cases (29%) had other etiologies. According to the Atlanta criteria, 19 patients (29%) were grouped as severe and 46 (71%) as mild pancreatitis (Table 1).

There were no significant differences between groups in terms of gender and age ($p=0.1$). Biliary etiology rates of pancreatitis were similar in both groups.

When procalcitonin levels and Ranson's and APACHE II scores at admission were compared, these values were found to be significantly higher

Table 1. Reasons why the patients were allocated to severe pancreatitis group

Causes	Multiorgan failure	Respiratory failure	Renal failure	Pancreatic necrosis	Infected necrosis	Pseudocyst formation	Metabolic disturbance
Patients (n=19)	5	11	5	6	8	2	9

in patients with severe pancreatitis than in those with mild pancreatitis ($p<0.001$) (Table 2). The procalcitonin levels of 39 patients with mild pancreatitis were determined on a daily basis and remained below 0.5 ng/ml from admission to discharge. The remaining seven mild pancreatitis patients had procalcitonin levels over 0.5 ng/ml (0.53-1.40) at the time of admission to hospital, but these levels decreased to below 0.5 ng/ml during the following days and remained normal thereafter. All 46 mild pancreatitis cases were treated without morbidity and mortality and discharged upon recovery. All the patients with severe pancreatitis had procalcitonin values over 0.5 ng/ml at the time of admission to hospital.

By computerized tomography only 10 of the 19 patients with severe acute pancreatitis had pancreatic necrosis. Eleven of the patients with severe acute pancreatitis died despite appropriate medical and surgical treatment; eight of the patients who died had pancreatic necrosis. Total mortality was 16%.

Sensitivity and specificity values for severe and mild acute pancreatitis patients calculated with procalcitonin level at 0.5 ng/ml, Ranson score at 3 and APACHE II score at 8 cut-off levels were

100%, 84% and 89%; and 84%, 63% and 89% respectively (Table 3).

In 19 patients with severe pancreatitis, the procalcitonin levels correlated with the severity and course of the disease. Eleven patients who died despite treatment had procalcitonin levels consistently over 0.5 ng/ml. However, 8 of 19 severe pancreatitis cases improved after appropriate surgical and medical treatment. Procalcitonin levels, which were higher at the beginning, gradually decreased and were within normal limits at discharge.

Repeated measurements ANOVA was applied to the procalcitonin results calculated in the first 6 days (Fig. 1). The procalcitonin values were found to be significantly higher in severe pancreatitis than in mild pancreatitis cases ($p=0.005$). Procalcitonin measurements displayed significant change over time, but there was no regular pattern of increase or decrease on particular days ($p=0.005$).

DISCUSSION

The most important step in the diagnosis and treatment of acute pancreatitis is differentiation between severe and mild cases. Contrasted dynam-

Table 2. Ranson's, APACHE II and procalcitonin values of patients (Mean±SEM)

Patient groups	Ranson	APACHE II	Procalcitonin (ng/ml)
Mild (n=46)	2.04±1.01*	4.8±1.63*	0.34±0.27*
Severe (n=19)	4.68±1.63	10.1±2.13	2.93±3.2

* $p<0.001$ (Mann Whitney U).

Table 3. The extent to which Ranson at 48th hour, APACHE II at 24th hour and procalcitonin at admission determine the severity of attacks

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Ranson	84	63	47	90	66
APACHE II	89	89	77	95	89
Procalcitonin	100	84	73	100	86

Calculation has been made from procalcitonin level at 0.5 ng/ml, Ranson score at 3, APACHE II score at 8 cut-off values; PPV: Positive predictive value; NPV: Negative predictive value.

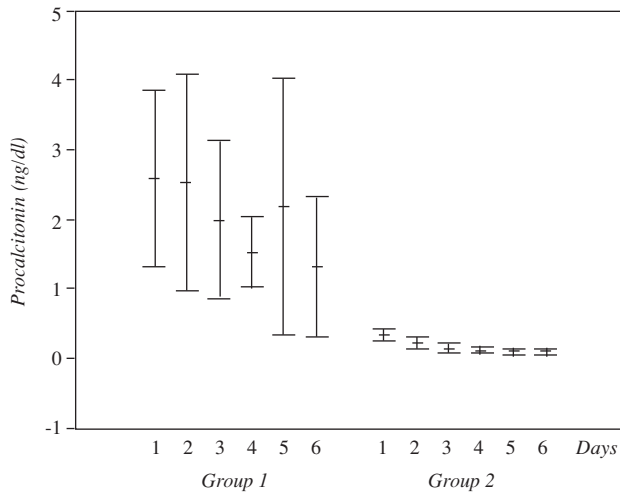


Fig. 1. Daily procalcitonin values of mild and severe acute pancreatitis cases in 95% interval.

(Group 1: Acute severe pancreatitis group; Group 2: Acute mild pancreatitis group; $p=0.005$ with ANOVA test.)

ic computerized tomography that shows pancreatic and peri-pancreatic necrosis is the gold standard in differentiating between acute edematous or necrotizing pancreatitis. Another advantage of computerized tomography is the possibility of taking percutaneous samples for bacterial investigation in the presence of necrosis.^[13,14]

Scoring systems are employed in order to determine the severity of acute pancreatitis as soon as possible and to identify any need for intensive care. To determine the Ranson score, which is used to establish the severity of pancreatitis, 11 parameters are evaluated and the waiting time is 48 h. The APACHE II scoring system, on the other hand, is an practical method that includes the patient's age and chronic disease state as well as 12 physiological values.^[4,15] Thus there is a recognized need for a method for determining the severity of acute pancreatitis which can be applied daily, can easily be evaluated, which is practical and has a high rate of specificity and accuracy.

In order to determine the prognosis of acute pancreatitis in advance, various markers such as α -2 macroglobulin, α 1-anti-trypsin, thrombomodulin, urinary trypsinogen activation peptide and CRP have been measured.^[7-9] Mantke et al.^[7] followed 73 acute pancreatitis cases with CRP and soluble thrombomodulin. On the third day of follow-up they reported that at the 75 ng/ml cut-off

level, thrombomodulin had 100% sensitivity, 73% specificity, 38% positive predictive value and 100% negative predictive value. At the 113 mg/dl cut-off level, CRP was 84% predictive, 60% specific, 78% positive predictive and 69% negative predictive in determining the severity of acute pancreatitis. These authors reported that differentiation between severe and mild pancreatitis could be made on the third day by measuring soluble thrombomodulin.^[7] In a multi-center study conducted in 2001, Mayer et al.^[9] monitored serum amyloid A levels in 137 mild and 35 severe acute pancreatitis cases for 5 days. They reported that serum amyloid A had 67% predictive sensitivity and 70% specificity in severe acute pancreatitis and that it was superior to CRP. It seems from these and similar findings that differentiating between severe and mild pancreatitis is not possible at the time of admission to hospital.

Procalcitonin is a glycoprotein that increases selectively in cases of bacterial inflammation, sepsis and multi-organ failure. In normal healthy individuals, procalcitonin is synthesized as the intracellular prohormone of calcitonin in the C cells of the thyroid gland and it is found at picogram levels in the plasma (~ 0.1 ng/ml). In cases of severe inflammations and sepsis, however, the plasma concentration ranges between 1 ng/ml and 1000 ng/ml; possible sources of this procalcitonin are neuroendocrine cells in the lungs and kidneys.^[10,11,16,17] Procalcitonin levels can be measured by immunoluminometric and radioimmunoassay methods or semi-quantitatively by strip tests. In this study the measurement was made by an immunoluminometric method.^[18-20]

In an experimental study in rats, Yonetci et al.^[21] found that procalcitonin and IL-6 combination might be a surrogate marker of infected pancreatic necrosis and should be preferred to other assay especially in severe acute pancreatitis. On the other hand Ammori BJ et al.^[22] studied the role of procalcitonin in gut barrier dysfunction in patients with acute pancreatitis and concluded that plasma concentrations of procalcitonin appear to reflect more closely the derangement in gut barrier function rather than the extent of systemic inflammation. In 2000, Rau et al.^[20] followed daily procalcitonin and CRP in a total of 61 acute pancreatitis patients, 22 of whom were edematous, 18 with sterile necrosis

and 21 with infected necrosis. These authors reported that in comparison to CRP, procalcitonin values were significantly superior for differentiating infected necrosis and that at the 1.8 ng/ml cut-off level, PCT had 94% specificity and 88% sensitivity. Kylanpaa-Back et al.^[19] measured procalcitonin levels semi-quantitatively with the PCT-Q test in 2001 and reported that they were more sensitive than CRP, Ranson and APACHE II criteria at the time of admission for determining the severity of acute pancreatitis. These authors found that procalcitonin had 92% sensitivity and 84% specificity. Ammori et al.^[18] measured calcitonin precursors at the time of admission by a radioimmunoassay method. At the 106 fmol/ml cut-off value, they identified severe septic complications and death with an accuracy rate of 94% and they showed that procalcitonin was better than APACHE II scoring in identifying the severity of pancreatitis. Frasqueti et al.^[23] concluded that early measurement of PCT, by means of a semiquantitative strip test, does not seem to be useful for predicting the severity of acute pancreatitis.

In cases of acute inflammation in the clinic, procalcitonin values increase and remain high for several hours following increases in interleukin-6 and TNF- α , but after the interleukin level decreases, procalcitonin begins to decrease as well.^[24,25] Riche FC et al.^[26] found that procalcitonin and IL-6 serum levels were elevated early in patients who eventually developed necrosis infection in severe acute pancreatitis cases that were divided into infected and noninfected necrosis groups according to computed tomography severity index. The level of procalcitonin is consistent with the clinical situation and the effectiveness of the treatment. A decrease in the elevated procalcitonin value is always a sign of improvement in the clinical picture, while absence of such a decrease shows that the critical situation is continuing.^[27-29] In a review by Werner et al,^[30] of all markers available today CRP is the gold standard in predicting the severity of acute pancreatitis, but procalcitonin seems to be a promising tool to monitor the progression of the disease. Procalcitonin levels in our study were consistent with this information. They were significantly higher in severe than in mild pancreatitis cases ($p=0.005$). The eleven mortal cases had high procalcitonin levels throughout, while the other eight who recovered had gradually decreasing and finally normal procal-

citonin levels. We consider these results as highly important for monitoring the prognosis of the disease and the effectiveness of treatment.

Procalcitonin level is a practical, simple parameter that can be measured both qualitatively and quantitatively in order to diagnose severe acute pancreatitis sooner and to monitor the clinical prognosis of the disease in addition to scoring systems. Therefore we believe that it can be adapted to routine clinical application.

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