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Changes and significance of early coagulation functions in patients with varying severities of acute pancreatitis.

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Abstract

The aim of this study was to investigate the early changes in coagulation functions in patients with different degrees of Acute Pancreatitis (AP). Data from a total of 133 AP patients was studied. The differences in the Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen Concentration (FIB), International Normalized Ratio (INR), and serum Ca^{2+} levels among different groups, and their relationships to the Acute Physiology and Chronic Health Evaluation (APACHE) II score were compared. FIB in the Moderately Severe Acute Pancreatitis (MSAP) group was significantly higher than the Control Group (CG), and the Mild Acute Pancreatitis (MAP) group ($P<0.05$). Ca^{2+} levels in the MSAP group were lower than in the control and MAP groups ($P<0.05$). PT, APTT, and INR in the Severe Acute Pancreatitis (SAP) group were higher than in the control, MAP, and MSAP groups ($P<0.05$). FIB in the SAP group was higher than in the control and MAP groups ($P<0.05$), and Ca^{2+} levels in the SAP group were lower than in the control, MAP, and MSAP groups ($P<0.05$). The APACHE II score in the MSAP group was higher than in the MAP and control groups ($P<0.05$), and higher in the SAP group than in the MSAP, MAP, and control groups ($P<0.05$). Ca^{2+} levels and the APACHE II score were negatively correlated in the MSAP group. In the SAP group, FIB was positively correlated with the APACHE II score, but Ca^{2+} levels were negatively correlated with them. In the classification of acute pancreatitis, FIB and Ca^{2+} levels are associated with the severity of pancreatitis. Patients with early AP show different levels of coagulation dysfunction, which is much more pronounced in patients with MSAP and SAP.

Keywords: Acute pancreatitis, APACHE II score, Coagulation functions, Ca^{2+}.

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Introduction

According to the latest revision of the Atlanta classification and definitions of acute pancreatitis by international consensus in 2012 [1], Acute Pancreatitis (AP) can be divided into Mild Acute Pancreatitis (MAP), Moderately Severe Acute Pancreatitis (MSAP), and Severe Acute Pancreatitis (SAP). SAP is often accompanied by severe complications, and even Multiple Organ Dysfunction (MODS), with studies showing that SAP has higher mortality (36-50 %), which can be even higher if accompanied by infections in the late stage [2]. In order to effectively treat AP in time, its severity needs to be assessed in the early stages, to guide treatment and predict prognosis. Accordingly, a series of scoring systems for evaluating AP have been introduced, one based on specific clinical indicators, and another on non-specific clinical physiological parameters [3,4]. Currently, the Computed Tomography (CT) grading, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Ranson score are widely used to predict the severity and prognosis of AP.

In recent years, both domestic and international studies have shown that pancreatic microcirculation disorders are critical early events in AP, and the fibrinolytic and coagulation systems are involved in this process [5-8]. However, there has been no research, in China or abroad, into how the coagulation changes correspond to the latest revisions of the pancreatitis classification systems. Therefore, in this study, we focused primarily on the early coagulation changes in patients with different severities of AP, with the aim of exploring the significance of the coagulation changes, and providing theoretical support for better prevention and treatment of AP-induced coagulation dysfunction.

Materials and Methods

Information

A retrospective study of 133 patients, admitted within 24 hours of the onset of AP to the Department of Gastroenterology and Hepatobiliary of the Affiliated Hospital and the Affiliated Baiyun Hospital of Guizhou Medical University, from October 2012 to March 2015, was undertaken. Any patients with malignant tumor or on oral anticoagulant drugs were excluded. The patients were divided into groups: mild AP (MAP, 49 patients), moderately severe AP (MSAP, 30 patients), and severe AP (SAP, 54 patients), according to the Atlanta 2012 clinical criteria for diagnosis and classification of acute pancreatitis. Patients with MAP do not have organ dysfunction, or local or systemic complications. MSAP patients have transient organ dysfunction and local or systemic complications but no persistent organ dysfunction. SAP patients have persistent organ dysfunction affecting single or multiple organs. A control group of healthy individuals (CG, 30 participants), with no bleeding or thrombotic disease, and who had not taken any medication for two weeks before the tests, was also recruited. There were no significant differences in gender or age between the groups (P>0.05). This study was conducted in accordance with the declaration of Helsinki, and it obtained the approval from the Ethics Committee of Guizhou Medical University. Written informed consent was obtained from all participants.

Initial examination

On the first day after admission, all subjects had body temperature, respiratory rate, blood pressure, and heart rate measured, and arterial blood gas analysis, serum electrolytes, liver and kidney function, routine blood and other tests performed.

Clinical indices

The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase or amylase activities at least three times greater than the upper limit of normal; (3) characteristic findings of acute pancreatitis on Contrast-Enhanced Computed Tomography (CECT), or less commonly Magnetic Resonance Imaging (MRI) or transabdominal ultrasonography. Mild acute pancreatitis has no organ failure, or local or systemic complications. Moderately severe acute pancreatitis is defined by the presence of transient organ failure within 48 h, and local or systemic complications. Severe acute pancreatitis is defined by persistent organ failure lasting longer than 48 h.

Treatment

Initial general treatment for all patients included fasting, gastrointestinal decompression, inhibition of pancreatic secretion using somatostatin 250 μg/h by continuous pump for 72 h, and intravenous infusion of imipenem/cilastatin 500 mg/500 mg 8 hourly. Patients with gallstones and obstruction had the obstructions relieved. Patients with hyperlipidemia were treated with small doses of low molecular weight heparin and insulin, or lipid adsorption for rapid lipid-lowering. All patients were given fluid resuscitation, early enteral nutrition support, and maintenance treatment for organ function in patients with complications.

Laboratory testing

A 2 ml sample of fasting peripheral venous blood was taken on the first morning after admission, of which 1.8 ml was well mixed with 0.2 ml of 3.2 % (w/v) sodium citrate, and used for immediate testing of coagulation functions (STA-R Evolution® automated coagulation analyser, STAGO Co., France). A second 2 ml of fasting peripheral venous blood was taken for immediate analysis of serum Ca^{2+} (ADVIA® 2400 Clinical Chemistry System, Siemens Co., Germany). The samples from the control group were taken on the day of their physical examination and tested using the same procedures as the above.

Statistical analysis

SPSS version 16.0 software (Chicago, SPSS Inc.) was used for statistical analysis. The measurement data were expressed as $\bar{x} \pm s$. The intergroup comparison used the analysis of variance, and when the overall mean values were not equal, further LSD-t-testing was performed for the pairwise comparison among multi-group data. The count data was expressed using the rate, and the comparison used the chi-square test, with the significance level $\alpha=0.05$. The correlation analysis of coagulation indexes with APACHE II scores used the Pearson analysis.

Results

Comparison of general information

The results in Tables 1 and 2 show there were no significant differences in gender and age (P>0.05), or in the time blood samples were taken after the onset of AP (P>0.05) between the groups. The control group fasted from 8 pm the day before, and blood was taken at 8 am on the day of physical examination.

Changes in coagulation functions and AP classification

Table 3 shows there was no significant difference in prothrombin time, activated partial thromboplastin time, fibrinogen concentration, international normalized ratio, or Ca^{2+} levels between the control and MAP groups (P>0.05). There was no significant difference in PT, APTT, or INR between the control, MAP and MSAP groups (P>0.05), but FIB in the MSAP group was significantly higher than in the control and MAP groups (P<0.05). Ca^{2+} levels in the MSAP group were significantly lower than the control and MAP

groups (P<0.05). PT, APTT, and INR in the SAP group were significantly higher than in the control, MAP, and MSAP groups (P<0.05). FIB was significantly higher in the SAP group than in the control and MAP groups (P<0.05), but only slightly higher than in the MSAP group, which was not statistically significant (P>0.05). Ca^{2+} levels in the SAP group were significantly lower than in the control, MAP, and MSAP groups (P<0.05).

Comparison of the APACHE II scores

The APACHE II scores (Table 4) show no significant difference between the control and MAP groups (P>0.05). The APACHE II scores in the MSAP group were significantly higher than in the control and MAP groups (P<0.05), and significantly higher in the SAP group than in the control, MAP and MSAP groups (P<0.05).

Correlations of PT, APTT, INR, FIB, and Ca^{2+} levels with APACHE II scores

The correlation analysis results are shown in Table 5. There was no linear correlation between PT, APTT, FIB, INR, and Ca^{2+} levels and the APACHE II score in the control and MAP groups. In the MSAP group, Ca^{2+} levels were negatively correlated with the APACHE II score (P<0.05, r=-0.639), and PT, APTT, FIB, and INR had no linear correlation with the APACHE II score. In the SAP group, FIB was positively correlated with the APACHE II score (P<0.05, r=0.654), and Ca^{2+} levels were negative correlated with the APACHE II score (P<0.05, r=-0.835). There was no linear correlation between PT, APTT, and INR and the APACHE II score in the SAP group.

Table 1. *Comparison of general information among different groups ($\bar{x}$ ± s, n).*

Group	Age (years)	Gender (M/F)
CG (N=30)	44.27 ± 16.72	18/12
MAP (N=49)	45.98 ± 14.25	35/14
MSAP (N=30)	42.30 ± 12.17	21/9
SAP (N=54)	46.28 ± 13.95	31/23
F/χ^2	0.602	2.872
P	0.615	0.412

Table 2. *The comparison of different groups in the blood sampling time after the onset of AP.*

Group	Blood sampling time (h)
MAP (N=49)	13.50 ± 3.65
MSAP (N=30)	14.10 ± 4.02
SAP (N=54)	14.60 ± 3.87
F	1.063
P	0.349

Table 3. *Comparison of coagulation-related indexes among different groups ($\bar{x}$ ± s).*

Group	PT (S)	APTT (S)	FIB (g/L)	INR (INR)	Ca^{2+} (mmol/l)
CG (N=30)	13.93 ± 3.39	27.61 ± 7.89	3.70 ± 1.60	1.25 ± 0.56	2.14 ± 0.41
MAP (N=49)	15.91 ± 5.26	28.73 ± 8.96	3.57 ± 1.54	1.31 ± 0.56	2.11 ± 0.44
MSAP (N=30)	16.90 ± 6.88	30.08 ± 12.24	4.81 ± 2.07^{ab}	1.33 ± 0.58	1.91 ± 0.34^{ab}
SAP (N=54)	21.77 ± 7.21^{abc}	34.88 ± 10.40^{abc}	5.38 ± 2.40^{ab}	1.76 ± 0.65^{abc}	1.62 ± 0.40^{abc}
F	13.697	4.816	8.998	7.18	16.586
P	<0.001	0.003	<0.001	<0.001	<0.001

Note: ^{a}Compared with group CG, P<0.05; ^{b}Compared with group MAP, P<0.05; ^{c}Compared with group MSAP, P<0.05.

Table 4. *Comparison of the APACHE II score among different groups ($\bar{x}$ ± s).*

Group	APACHE II score	F	P
CG (N=30)	5.77 ± 1.10	153.684	<0.001
MAP (N=49)	6.06 ± 1.16		
MSAP (N=30)	10.80 ± 2.01^{ab}		
SAP (N=54)	12.43 ± 2.34^{abc}		

Note: ^{a}Compared with group CG, P<0.05; ^{b}Compared with group MAP, P<0.05; ^{c}Compared with group MSAP, P<0.05.

Table 5. *Correlations of PT, APTT, INR, FIB, and Ca^{2+} with APACHE II score.*

Group	PT	APTT	FIB	INR	Ca^{2+}
CG (N=30)	0.066	-0.181	-0.295	-0.029	-0.008
MAP (N=49)	-0.135	-0.033	0.142	-0.059	-0.206
MSAP (N=30)	-0.205	0.021	-0.014	0.022	-0.639**
SAP (N=54)	-0.041	0.139	0.654**	-0.07	-0.835**

Note: **P<0.01.

Discussion

The currently recognized theories on the pathogenesis and evolution of pancreatitis include not only trypsin self-digestion [9,10], white blood cell activation, cascade of inflammatory cytokines, apoptosis, and overload of intracellular calcium in pancreatic acinar, but also the theory of pancreatic microcirculation disturbance, which plays an important role in it. Maeda et al. [11] confirms that activated pancreatin in pancreatic trypsin is a prerequisite for local inflammation of the pancreas.

In AP, kallikrein can transform kallikreinogen into kinin and bradykinin, thus increasing vasodilation and permeability, leading to microcirculation disorders. Particularly in the SAP group, abnormal coagulation parameters are significantly associated with the severity of the AP. The early coagulation functions in SAP patients show a hypercoagulable state in the blood, followed by secondary activation of the fibrinolysis system, which may be related to the changes in the relevant cytokines, and this is the main cause of microcirculation disorder in AP. Therefore, when SAP occurs, if the patient's microcirculation disorders cannot be corrected timeously, it can affect multiple organs, and cause MODS [12,13].

It is well known that platelets, blood vessel walls, coagulation factors, anticoagulant factors, the fibrinolytic system, hemodynamic integrity, and the physiological regulation and balance between them, are all involved in the normal mechanisms of coagulation. The activation of coagulation factors is a chain cleavage reaction. The hemostatic roles of coagulation factors include three pathways, namely the intrinsic coagulation pathway, the extrinsic coagulation pathway, and the common coagulation pathway. In addition, we know that PT and APTT are sensitive indices, which can reflect the exogenous and endogenous coagulation functions, and shortening of PT and APTT can suggest that the patient is in a hypercoagulable state, and indicate clotting mechanism disorder [5]. Among many indices for clinically detecting the coagulation functions, the current most commonly used include PT, APTT, FIB, and INR.

In our study, we found that in the SAP group, PT, APTT, and INR are obviously prolonged compared with the control, MAP, and MSAP groups, which can indicate that patients with SAP may have clotting mechanism disorders. In this study, those in the MSAP and SAP groups show statistically significant differences from the MAP and control groups, but FIB in the MSAP and SAP groups showed no significant difference, indicating that patients with MSAP and SAP may be in a hypercoagulable state in the early stages of AP, which implies FIB can be used as a reference index to assess the severity of AP. This study showed that the serum Ca^{2+} levels in the MSAP and SAP groups are significantly reduced compared with the MAP group. Studies have shown that the overload of intracellular calcium in pancreatic acinar is an important mechanism underlying the large amounts of pancreatin secreted in the early stages of AP [14]. The mechanisms of pancreatic acinar cell injury include autophagy activated by zymogen, oxidative stress injury, calcium overload, and the influx of extracellular calcium, which is one of the most important factors in calcium overload. In addition, it has been confirmed recently that the release of various cytokines in patients with SAP, such as Tumor Necrosis Factor (TNF)-α [15], interleukin (IL)-1, or IL-6 can cause a decrease in serum Ca^{2+} concentration. Kawa et al. [16] proposes that hypocalcemia is an early sensitive index of MODS in SAP patients. This study also confirms that the serum Ca^{2+} concentration is negatively correlated with the severity of AP. It confirms that Ca^{2+} plays a vital role in the progression of pancreatitis from mild to moderate, and then severe acute pancreatitis, in the early stages.

Current research has shown that in patients with acute critical conditions, endothelial cell injuries caused by a variety of conditions can activate both intrinsic and extrinsic coagulation systems, as well as cause coagulation and fibrinolysis system disorders, thus exacerbating disease progression [17-20]. It is recognized that the APACHE II scoring system is an important indicator when evaluating disease severity and predicting prognosis and mortality; the higher the score, the more severe the disease, and worse is the prognosis [21]. Given the APACHE II scoring system has been widely recognized for its reliability in determining the condition and prognosis of AP patients [22], it is important in assessing the severity of AP. This study shows that in AP, the APACHE II scores in the MSAP and SAP groups are significantly different from those in the MAP and control groups, and the comparison of APACHE II scores between the MSAP and SAP groups also shows statistically significant differences, indicating that the APACHE II score is positively correlated with the disease severity; the higher the APACHE II score, the more severe the AP conditions.

The APACHE II scoring system has been widely accepted for evaluating AP patients, but has some limitations, including its lack of indices for evaluating the coagulation functions. It is rarely reported in China and abroad that coagulation-related indices are introduced into the APACHE II scoring system. In this study, looking at correlations between coagulation functions and Ca^{2+} levels and APACHE II scores in AP patients shows that in the SAP group, PT, APTT, and INR have no linear relationship with the APACHE II score, but FIB is positively correlated with it, indicating that FIB is significantly increased, and the higher the APACHE II score, the more severe the AP conditions. Results from Ou et al. [23] and Yue et al. [24] are consistent with ours, indicating that in SAP, FIB is linearly correlated with the APACHE II score. In this study, we found that Ca^{2+} levels in the MSAP and SAP groups are negatively correlated with the APACHE II score, indicating that the lower the Ca^{2+} concentration in AP patients, the higher the APACHE II score, and the more severe the AP conditions. Therefore, the reduction in Ca^{2+} levels in AP patients can be used as an index to evaluate the disease severity, and this study confirms the accuracy of the classical Ranson and Glasgow standards, which use Ca^{2+} as a scoring index in AP.

The study shows that the early coagulation changes in different degrees of AP are different, so it further validates the theory that coagulation changes also play important roles in the evolution of AP. The possible reasons for this may be the fact that the patients in the MAP group have relatively mild disease conditions, so damage to the coagulation system is relatively minor, but early testing can detect obvious abnormalities. In the MSAP group, although patients exhibit transient organ failure, they recover spontaneously, as the clotting mechanism is still in a state that allows compensation, namely the coagulation changes are not clear yet. In the SAP group, the early coagulation functions show abnormalities, which may be because early severe microcirculation disorders have already occurred in these patients. Therefore, detecting abnormalities in the coagulation functions will have greater significance in evaluating severity in the patients with MSAP and SAP.

The APACHE II score is currently an important index for judging the severity of diseases [25], as well as judging the severity of AP. We found that the higher the APACHE II score, the more severe the AP conditions were. Currently, both Chinese and international practitioners use an APACHE II score of ≥ 8 points as the index for moderate and severe AP, and there is no clear dividing line between the moderate and severe AP.

This study shows that FIB in the SAP group is linearly correlated with the APACHE II score, and Ca^{2+} levels in the MSAP and SAP groups are linearly correlated with the APACHE II score. This indicates that early detection of FIB and Ca^{2+} abnormalities in SAP patients will have important clinical significance with respect to judging the severity and prognosis of the AP, and provide help in understanding the microcirculation disorders in AP patients. It can also provide help in the early prevention of MODS; provide a basis for correcting coagulation disorders and improving the prognosis, so the cure rate in AP can be improved. Further studies on the relationship between coagulation and the severity of acute pancreatitis (organ failure and recurrence) are planned.

Conclusions

In the new classification of acute pancreatitis, FIB and Ca^{2+} levels are associated with the severity of the pancreatitis. Patients with early AP exhibit different levels of coagulation and serum Ca^{2+} abnormalities, which are much more obvious in the patients with MSAP and SAP, and early detection of coagulation functions may be significant in assessing the severity. A higher APACHE II score indicates more severe AP conditions.

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Conflict of Interest

All authors have no conflict of interest regarding this paper.

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