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Effect of Chaiqinchengqi decoction on serum amyloid A in severe acute pancreatitis patients

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ABSTRACT

Objective: To investigate the effect of Chaiqinchengqi decoction (CQCQD) on serum amyloid A (SAA) in severe acute pancreatitis (SAP) patients. **Methods:** Thirty-five participants enrolled and were randomly assigned into either a treatment condition (n=17, treated with CQCQD) or a control condition (n=18, treated with placebo) 24 hours following the onset of the disease. No statistical difference was observed in either group at baseline. Upon admission, the Acute Physiology and Chronic Health Evaluation score Ⅱ (APACHE Ⅱ), SAA, serum C-reactive protein (CRP) and interleukin-6 (IL-6) were measured, as well as on the first, 3rd and 7th day and were compared between the two groups. Organ complications, infection, operation rate, mortality and hospital stay were also compared. **Results:** The duration of acute respiratory distress syndrome, acute hepatitis, acute renal failure, gastrointestinal failure and blood coagulation dysfunction were shorter in the treatment group than in those in the control group (P < 0.05). The secondary infection rates and the hospital fees in the treatment group were lower than those in the control group (P < 0.05) as well as length of hospital stay (P < 0.01). After 3 days of hospitalization, the APACHE Ⅱ, score SAA levels, serum CRP and IL-6 in the treatment group was lower than those in the control group (P < 0.05). SAA was positively correlated with serum CRP (R = 0.346, P = 0.042), Ranson score (R = 0.442, P = 0.008) and serum IL-6 (R=0.359, P =0.034). The area under the receiver operating characteristic curve of admission SAA predict pancreatic necrosis (PN) was 0.815 (95% *CI*: 0.625-0.954; P =0.006). The best cut-off value of admission SAA was 7.85 mg/L with the sensitivity 84.6% and specificity 68.2%. **Conclusions:** The CQCQD can reduce the duration of organ damage through lowering the SAA in SAP patients and the SAA can early predict the PN and severity of SAP patients.

1. Introduction

The morbidity of acute pancreatitis (AP) is 5.4-79.8/10 million[1,2]. Severe acute pancreatitis (SAP) accounts for 20%-30% with 10%-56% mortality[3-6]. 20%-40% of patients die from multiply organ failure induced by the systemic inflammatory response syndrome in the early stages[7-11]. Serum amyloid A (SAA) C-reactive protein (CRP), which is an acute phase response protein, increase after 4-6 hours of AP onset and sharply increase to a peak of more than 1 000-2 000 times normal after 24-48 hours during the development of systemic inflammatory response syndrome (SIRS)[12]. Elevated SAA is involved in early inflammation and tissue damage through stimulating the cytokines TNF-a, IL-6 and IL-8 released from polymorphonuclea cells[13]. Mayer *et al*[14] found that SAA was a better early predictor of severity than CRP in acute pancreatitis.

Chaiqinchengqi decoction (CQCQD) is modified from Dachengqi Decoction[15], which is a traditional Chinese medicine prescription and is traditionally used as purgatives in China. In recent decades, it has widely been used for AP[16]. Our study had found that CQCQD could effectively improve the symptoms, reduce diffusion and proliferation, reduce complications and mortality[14] through protecting organ function via the suppression of SIRS[17-19]. However, there are no studies concerning the effect on SAA.

The aim of the present study was to investigate the effect of CQCQD on SAA in SAP patients.

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2. Materials and methods

2.1. Inclusive criteria

Male and female SAP patients (≥18 and ≤70 years of age) hospitalized within 24 hours of onset of symptoms were enrolled. The diagnostic criteria formulated for SAP at the Bangkok World Congress of Gastroenterology 2002 in Thailand were adopted[2].

2.2. Exclusion criteria

Patients with any of the following were excluded from the study: concurrent sepsis or pancreatic infection or peripancreatic infection caused by a second disease; those sent directly to the intensive care unit for multiorgan failure, post-encoscopic Retrograde Cholangio-Pancreatography or traumatic or operative pancreatitis; pregnancy, malignancy, immunodeficiency or moribund patients regardless of cause within 48 hours prior to enrollment.

2.3. Withdrawal criteria

Patients who had been enrolled in the study could be withdrawn if: the patient died or received an operation because they were not responsive to intensive care treatment within 72 hours upon admission; the patient could not continuously receive traditional Chinese medicine treatment due to adverse reactions or they strongly requested to withdraw from the study due to other reasons.

2.4. Preparation of CQCQD

Chinese medicinal herbs in CQCQD were provided by West China Hospital and included Chaihu (*Radix bupleuri*) 15 g, Huangqin (*Radix scutellariae*) 15 g, Houpu (*Cortex magnoliae officinalis*) 15 g, Zhishi (*Fructus aurantii immaturus*) 15 g, Dahuang (*Radix et rhizoma rhei*) 15 g, Danpi (*Cortex moutan*) 9 g, Yuanhu (*Rhizoma corydalis*), Chuanlian (Chinaberry fruit) 9 g, Gansui (*Radix kansui*) 0.2 g and Mangxiao (*Natrii sulfas*) 10 g. Every decoction was made into particle preparation (2 bags×10 g). Before the experiment, the particle preparation of CQCQD was prepared for a solution (200 mL/10 g).

The placebo was similar with CQCQD in packaging, shape, smell, color and so on.

2.5. Study Design

The study was conducted in West China Hospital of Sichuan University. Patients enrolled in the study were randomly assigned into the study group or the control group by random numbers (1:1) generated using SAS software. The patients in the treatment group were administered with QCQCQD by gastric perfusion (50 mL/2 h×7) and retention enema (200 mL/6 h×7). Patients in the control group received the same volume and concentration via the same methods as the treatment group with placebo treatment.

All patients received standardized comprehensive treatment by the same group of physicians as follows[20,21]: intensive care, oxygen inhalation, fluid resuscitation to correct fluid losses in the third space and maintain adequate intravascular volume as well as homeostasis of electrolyte and acid-base, fasting and gastrointestinal decompression as well as H_2-blocking agent or proton pump inhibitor, prophylactic antibiotics for 7-14 days, nutritive administration, respirator administration if hypoxemic respiratory failure developed, and symptomatic treatment. Patients were observed during their hospital stay. Follow-up evaluations, including an abdominal ultrasound and short questionnaire regarding abdominal pain and daily activities, were performed for up to 3 months following discharge.

The following parameters were measured: SAA, serum CRP, serum IL-6, the initial Balthazar's CT score, the APACHE Ⅱ score obtained upon admission as well as those obtained onthe first, 3rd and 7th day, incidence and duration of complications including acute respiratory distress syndrome (ARDS), acute renal failure (ARF), acute hepatitis (AH), encephalopathy (EP), gastrointestinal failure (GF), blood coagulation dysfunction (BCD): infection rate, hospital stay, operation rate and mortality.

The concentration of SAA and serum IL-6 were measured with ELISA kits (ADL, United States of America) according to the instructions by the manufacturers.

Diagnostic criteria for organ failure were as follows[22,23]:

AHF: hypotension, heart rate≤54 b.p.m., or >130 b.p.m., mean arterial pressure≤ 6.5 kPa (49 mmHg);

ARDS: dyspnea, R > 35 b.p.m., PaO_2 < 8.0 kPa (60 mmHg);

ARF: urinary volume < 480 mL/24 h (20 mL/h) or serum creatinine ≥177 μmol/L (2 mg/dL);

AH: serum bilirubilin ≥34 μmol/L, ALT > 2 times of the upper normal limit;

EP: neurologic failure if mental confusion, delirium or coma;

GF: paralytic ileus, hematemesis or melena, bleeding volume > 1 000 mL;

BCD: platelet count was ≤ 80× 10^9/L, PT > 16 s, APTT > 45 s, FIB < 1.5 μ 2.0 g/L.

2.6. Statistical analysis

Data were expressed as mean±SD or percentage. Data in normal distribution was analyzed using *t*-test; data in non-normal distribution was analyzed using Wilcox on rank sum test. Categorical data was analyzed using *chi*-square test. For calculation of cut-off values, positive predictive values (PPV), area under the curve (AUC), sensitivity and specificity, and receiver-operator characteristics (ROC) analyses were performed. $P < 0.05$ was considered statistically significant.

The medical ethics committee of West China Hospital at Sichuan University approved this study. All patients gave their informed consent, and the study was conducted according to the recent principles of the Declaration of Helsinki (World Medical Association, 2000).

3. Results

3.1. Clinical characteristics

From March 1, 2009 to July 31, 2009, there were 389 patients with AP hospitalized in our Center who were initially screened for entry into the study. A total of 78 patients met the diagnostic criteria of SAP, of which 35 patients who met the selective criteria of the study were enrolled into the study (17 in treatment group and 18 in control group). No patients were withdrawn due to loss of follow-up. No patients had verified evidence of adverse effects.

There were no statistical differences between the two groups in sex, age or etiology ($P > 0.05$), nor in the 48-h Ranson score, admission APACHE II score and Balthazar CT scores in the initial stage of hospitalization ($P > 0.05$, Table 1).

Table 1
Baseline data of the control group and the treatment group.

Baseline data		Control group (n=17)	Treatment group (n=18)
Sex(M/F)		11/9	9/8
Age (year)		48.5±12.2	49.4±8.5
Pathogen [(n)%]	Cholelithiasis	5(29.4)	6(33.3)
	Alcoholism	3(17.6)	2(11.1)
	Hyperlipidemia	3(17.6)	4(22.2)
	Idiopathic	6(35.3)	6(33.3)
Ranson score (mean±SD)		4.2±1.9	3.8±1.5
Admission APACHE II score (mean± SD)		10.3±6.7	8.9±4.3
Balthazar CT score (mean±SD)		4.9±1.2	4.9±1.5

3.2. Complication

There were no statistical differences between the two groups in the incidence of organs dysfunction (P > 0.05, Table 2), but the duration of ARDS, ARF, AH, GF and BCD in treatment group were significantly shorter than those in the control group (P < 0.05, Table 3).

Table 2
Incidence of the complication in the treatment and the control group[(n)%].

Complication	Treatment group (n=17)	Control group(n=18)
Shock	3(17.7)	6(33.3)
ARDS	10(58.8)	14(77.8)
ARF	3(17.7)	3(16.7)
AH	6(35.3)	8(44.4)
EP	2(11.8)	2(11.1)
BCD	4(23.5)	3(16.7)
GF	6(35.3)	7(38.9)

Table 3
Duration of complications in the treatment and the control group (d).

Complication	Treatment group (n=17)	Control group(n=18)
Shock	1.7±1.2	3.5±2.4
ARDS	2.8±1.8	5.8±3.9[a]
ARF	2.1±0.5	5.3±2.3[a]
AH	2.5±2.1	5.2±1.9[a]
GF	4.9±2.5	8.2±5.1[a]
BCD	2.5±1.3	16.7±9.0[a]
EP	3.7±1.5	4.3±1.8

a:P < 0.05 *vs*. treatment group.

Table 4
Prognosis in the treatment group and the control group.

Prognosis	Treatment group (n=17)	Control group (n=18)
Secondary infection [(n)%]	2(11.8)	8(44.4)[b]
Operation [(n)%]	0(0)	1(5.6)
Hospital stay (mean± SD)	17.8±8.8	27.8±7.9[d]
Death [(n)%]	1(5.9)	1(5.6)
Hospital fees (RMB)	31 891.0±18 895.4	64 365.5±51 377.6[f]

b: P < 0.01 *vs*. treatment group; d: P < 0.01 *vs*. treatment group; f: P < 0.01 *vs*. treatment group.

3.3. Prognosis

Secondary infection rates and hospital fees were lower in the treatment group than those in the control group (P < 0.05). Hospital stay was also shorter in the treatment group (P < 0.01, Table 4).

3.4. APACHE Ⅱ score, SAA, serum IL-6 and serum CRP in the treatment group and control group

There were no statistical differences between the two groups in the admission and first-day APACHE Ⅱ score, SAA, serum IL-6 and CRP (P > 0.05). After 3 days of hospitalization,, the APACHE Ⅱ score, SAA, serum IL-6 and CRP in the treatment group were significantly lower than those in the control group (P < 0.05).

There were no statistical differences in admission and first-day APACHE Ⅱ between the treatment group and the control group (9.3±4.4 *vs*. 11.5±6.7; 8.9±4.9 *vs*. 10.7±5.7, P > 0.05). On the 3rd and 7th day, the APACHE Ⅱ in the treatment group was lower than the control group (6.5±3.5 *vs*. 10.3±3.9; 5.6±3.5 *vs*. 9.5±4.4, P < 0.05).

There were no statistical differences in admission and first-day serum IL-6 between the treatment group and the control group (162.5±48.1 *vs*. 156.1±53.3; 151.3±34.9 *vs*. 153.4±34.5, P>0.05). But on the 3rd and 7th day, the serum IL-6 in the treatment group was lower than those in the control group (119±33.1 *vs*. 149.8±36.1; 87.3±30.9 *vs*. 129.7±34.7, P < 0.05).

There were no statistical differences in admission and the first-day SAA between the treatment group and the control group (7.2±3.7 *vs*. 7.8 ±2.5; 6.2±2.3 *vs*. 6.5±3.9, P > 0.05). On the 3rd and 7th day, the SAA in the treatment group was lower than those in the control group (4.9±2.5 *vs*. 6.3±2.3; 4.6±2.2 *vs*. 6.1±3.1, P < 0.05).

There were no statistical differences in admission and first-day serum CRP between the two groups (179.8±43.1 *vs*. 181.3±46.0; 183.2±45.3 *vs*. 185.1±42.7, P>0.05). On the 3rd and 7th day, the SAA in the treatment group was lower than those in the control group (120.1±47.9 *vs*. 156.9±45.9; 91.5±33.6 *vs*. 138.7±36.2, P<0.05).

3.5. Relationship of serum SAA with severity index of SAP

Correlation analysis found that the SAA was positively correlated with serum CRP (R=0.346, P=0.042), Ranson score (R=0.442, P=0.008) and serum IL-6 (R=0.359, P=0.034, Figure 1). In the 35 SAP patients, the receiver operating characteristic (ROC) curve of admission serum SAA was analyzed with pancreatic necrosis as a positive indicator and non-pancreatic necrosis as a negative indicator according the result of enhance CT. The AUC was 0.815 (95% *CI*: 0.625-0.954; P = 0.006, Figure 2). The PPV analysis also found that the best cut-off value of admission SAA predicting the pancreatic necrosis of was 7.85 mg/L with the sensitivity 84.6% and specificity 68.2%.

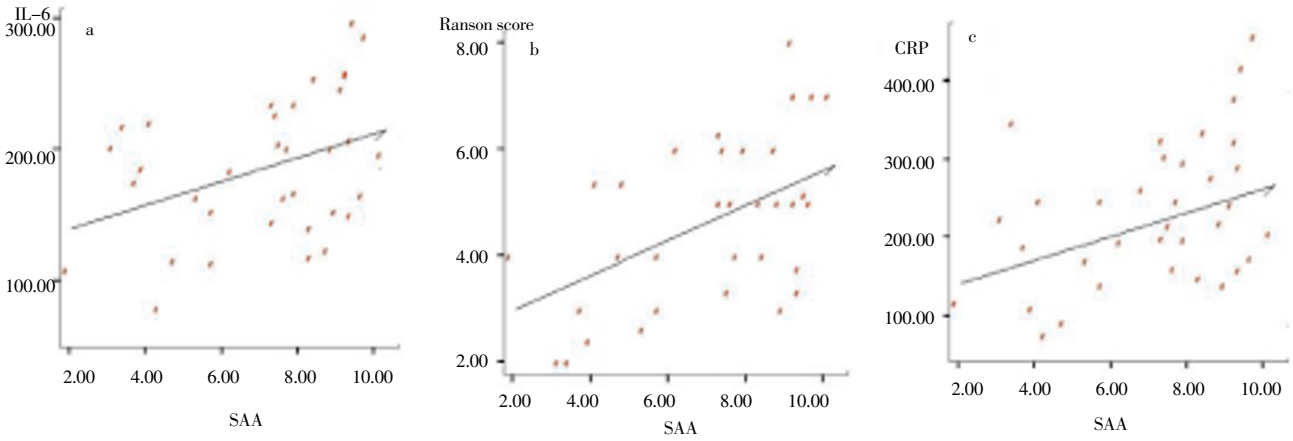

Figure 1. Scatter diagram of admission SAA and serum IL-6 (a), Ranson score (b) and admission serum CRP (C).

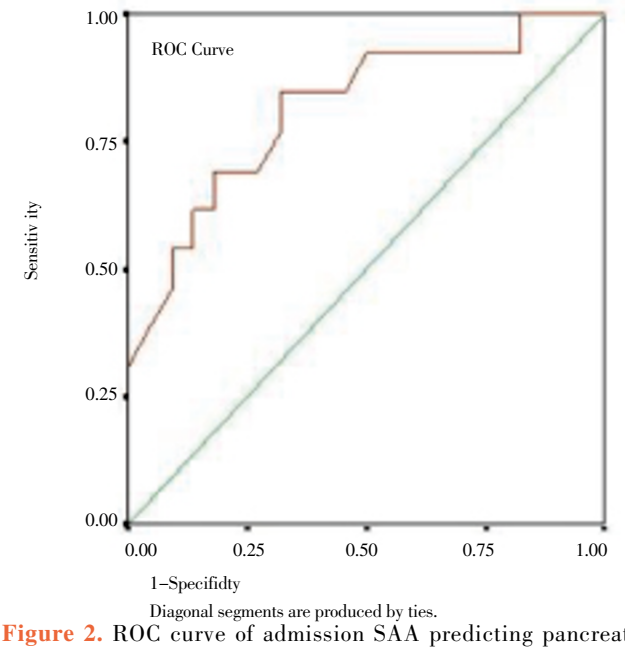

Figure 2. ROC curve of admission SAA predicting pancreatic necrosis.

4. Discussion

The mortality of SAP was 10%- 30%[1-4]. 20%-40% of those patients died in MODS induced by SIRS in the early stage[5-9]. In the course of occurrence and development of SIRS, the SAA is one of the acute phase response proteins comprising a family of apolipoproteins which are mainly synthesized in the liver in response to cytokines following acute-phase stimulus such as physical injury or infection[24,25], increased after 4-6 hours of disease onset, and sharply rose to a peak of more than 1 000-2 000 times normal after 24-48 hours[12]. The elevated SAA involved in early inflammation and tissue damage through stimulating the elevation of inflammatory factors such as TNF-a, IL-6 and IL-8 released from polymorphonuclea cell. The SAA in the patient complicated with pancreatic necrosis, pancreatic necrosis infection or MODS was higher and a marker of early prediction of severity of AP[14,26-33]. The results of our study were consistent with this conclusion. We found that the SAA was positively correlated with serum IL-6 (R = 0.359, P = 0.034) and the severity index of SAP including the serum CRP (R = 0.346, P = 0.042), APACHE II score (R = 0.367, P = 0.030) and Ranson score (R = 0.442, P = 0.008). The ROC curve of admission SAA was analyzed with pancreatic necrosis as positive indicators and non- pancreatic necrosis as negative indicators according to the result of the enhanced CT; the area under the ROC curve is 0.815 (95% *CI*: 0.625-0.954; P=0.006). The PPV analysis also found that the best cut-off value of admission SAA predicting the pancreatic necrosis of is 7.85 mg/L with the sensitivity 84.6% and specificity 68.2%. The results indicated that the SAA not only can predict the PN but also the severity in SAP patients.

CQCQD modified from Dachengqi Decoction (Houpu, Zhishi, Dahuang and Mangxiao) was the commonly used herbal prescription in the treatment of SAP in the early stage in China. It can effectively improve the symptoms and signs, reduce proliferation and reduce the incidence of complications and mortality of SAP patients through protecting intestinal mucosal barrier and organ function, suppressing SIRS, helping the restoration of injured pancreas and the absorption of peripancreatic inflammation and improving microcirculation of pancreas. In this study, we also found that the duration of ARDS, ARF, AH, GF and BCD in the treatment group were shorter than those in the control group ($P < 0.05$). The secondary infection rates and the Hospital fees in the treatment group were lower than those in the control group ($P < 0.05$) as well as the length of the hospital stay ($P < 0.01$).

Based on the therapeutic effect of CQCQD on SAP patients and the status of SAA in SIRS and organ injury, the present study on 35 SAP patients was to investigate the hypothesis that CQCQD could reduce the SAA, relive the SIRS, and then cut down the MODS of SAP patients. Through comparison with the serum CRF and the APACHE II score, an important diagnostic and predictable severity indicator of SAP[34-36], we found that the SAA and serum CRP and IL-6 and the APACHE II score atadmission and the first day were not significantly different between the CQCQD treatment group and the control group. However, on the 3rd day and 7th day after admission, the SAA and serum CRP and IL-6 concentration and the APACHE II score in the treatment group were lower than those in the control group ($P < 0.05$). This result indicated that mechanism of the CQCQD reliving the severity of SAP might result from reducing the SAA.

In conclusion, our study indicated that CQCQD can reduce the severity and shorten the duration of organ dysfunction of SAP by lowering the SAA. However, due to the limitations of sample size, our study failed to find an impact on incidence and mortality. In addition, the specific mechanism of CQCQD reducing the SAA is still in need of further study.

Conflict of interest statement

We declare that we have no conflict of interest.

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