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Changes of Serum Procalcitonin (PCT), C-Reactive Protein (CRP), Interleukin-17 (IL-17), Interleukin-6 (IL-6), High Mobility Group Protein-B1 (HMGB1) and D-Dimer in Patients with Severe Acute Pancreatitis Treated with Continuous Renal Replacement Therapy (CRRT) and Its Clinical Significance

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDG 1 **Ning Gao***
BCDG 2 **Chengjun Yan***
AEF 1 **Guochang Zhang**

1 Department of Intensive Care Unit, Jining No. 1 People's Hospital, Jining, Shandong, P.R. China
2 Department of Emergency, Jining No. 1 People's Hospital, Jining, Shandong, P.R. China

* Co-first authors

Corresponding Author: Guochang Zhang, e-mail: guochangzhang6@163.com

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Background: The aim of this study was to investigate the changes in serum levels of procalcitonin (PCT), C-reactive protein (CRP), interleukin-17 (IL-17), interleukin-6 (IL-6), high mobility group protein-B1 (HMGB1), and D-dimer in severe acute pancreatitis (SAP) patients during treatment with continuous renal replacement therapy (CRRT) and the clinical significance.

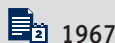
Material/Methods: A total of 92 SAP patients admitted to our hospital from January 2017 to December 2017 were selected and randomly divided into the observation group and the control group using a random number table method, with 46 cases in each group. The control group was given conventional therapy, and the observation group was given CRRT in addition to conventional therapy.

Results: After 1 week, the total effective rate of treatment in the observation group was significantly higher than that in the control group ($P < 0.05$). In the observation group, each index showed a continuous downward trend at 6, 12, and 24 hours after treatment, and at different time points after treatment, the indexes were significantly lower than those in the control group ($P < 0.05$).

Conclusions: CRRT is more effective in the treatment of SAP, and its effects are more obvious in removing a variety of inflammatory factors and reducing the serum levels of PCT, HMGB1, and D-dimer, which is of great clinical significance.

MeSH Keywords: **HMGB1 Protein • Interleukin-17 • Pancreatitis • Receptors, Interleukin-6**

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Background

Pancreatitis is a clinically common serious disease of the digestive system caused by chemical lesion of pancreatic tissue autodigestion [1]. With changes to people's dietary structure and habit, the incidence rate of pancreatitis is increasing year by year, and its incidence is acute and rapid. Pancreatitis can be divided into mild acute pancreatitis (MAP), moderate severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP) according to the severity. There are many complications of SAP, often accompanied by excessive release of inflammatory mediators, thereby causing peritonitis, pyemia, and so on, and causing damage and dysfunction to distant organs, such as acute renal failure and multiple organ dysfunction syndrome, resulting in a high patient mortality rate [2,3]. During the pathogenesis of SAP, the immune system is activated, releasing a large number of inflammatory mediators such as C-reactive protein (CRP), interleukin-17 (IL-17), and interleukin (IL-6), triggering an inflammatory cascade reaction, leading to bacterial translocation and secondary injuries to distant tissues and organs, releasing procalcitonin (PCT) continuously, and causing systemic inflammatory response [4]. A study found that the levels of high mobility group protein B1 (HMGB1) and D-dimer were related to the severity of SAP and the prognosis of patients [5]. Continuous renal replacement therapy (CRRT) is a new model of renal replacement therapy and was first applied in the clinical treatment of simple renal failure. With the transformation of the treatment mode of acute pancreatitis to comprehensive treatment, CRRT plays a significant role in the treatment of SAP [6]. In our study, the effects of CRRT on the levels of PCT, CRP, IL-17, IL-6, HMGB1, and D-dimer were analyzed in the treatment of SAP patients with CRRT, in order to provide a basis for recommended treatment of SAP.

Material and Methods

General data

A total of 92 SAP patients admitted to our hospital from January 2017 to December 2017 were included in the study. Inclusion criteria were: 1) patients complying with SAP diagnostic criteria [7], who have pancreatic enlargement and peripancreatic fluid exudation shown in imaging examination, 2) patients with Acute Physiology and Chronic Health Evaluation (APACHE) II score of more than 8 points, and 3) patients who signed the informed consent. Exclusion criteria were: 1) patients with autoimmune diseases, or 2) pancreatic cancer patients. Patients were divided into the control group and the observation group by random number table method, with 46 cases in each group. There were no significant differences in general data between the 2 groups of patients ($P>0.05$) (Table 1).

Treatment

The control group received conventional therapy, including fasting, gastrointestinal decompression, nutritional support, rehydration correction of water electrolyte, acid-base balance, and so on. Infection patients were treated with anti-infective therapy, and all patients were given intravenous ulinastatin (manufacturer: Techpool Bio-pharma Co., Ltd., Guangdong, registered number: NMPN H19990133) at 100 000 U dissolved in 500 mL 0.9% sodium chloride solution, administered by intravenous drip twice daily for 7 days.

The observation group was treated with CRRT on the basis of the treatment of the control group. The ADM08/ABM type CRRT machine (Fresenius, Germany) was used. After the displacement fluid (manufacturer: Shanghai Changzheng Fumin Jinshan Pharmaceutical Co, Ltd., composition: Ca^{2+} 1.88 mmol/L, K^+ 2.0 mmol/L, Na^+ 135 mmol/L, Mg^{2+} 0.75 mmol/L, Cl^- 108 mmol/L, lactate 33.75 mmol/L, and glucose 1.5 g/L) was diluted, the

Table 1. General data of research objects.

Data	Observation group (n=46)	Control group (n=46)	t/χ^2	p
Sex (male/female)	24/22	22/24	0.044	0.835
Age (years old)	20~65	20~60		
Average age (years old)	38.87±6.47	39.13±6.56	0.191	0.849
APACHE II score before treatment	18.75±3.04	18.93±3.16	0.278	0.782
Cause of disease [n (%)]				
Hyperlipemia	20 (43.48)	18 (39.13)	0.989	0.804
Alcoholism	16 (34.78)	14 (30.43)		
Cholelithiasis	7 (15.22)	9 (19.57)		
Others	3 (6.52)	5 (10.87)		

Table 2. Comparison of curative effects between two groups of patients (n, %).

Group	n	Cured	Markedly effective	Effective	Ineffective
Observation group	46	21 (45.65)	11 (23.91)	9 (19.57)	5 (10.87)
Control group	46	10 (21.74)	8 (17.39)	16 (34.78)	12 (26.09)

Rank sum test of curative effects of two groups of patients: $z=2.326$, $p=0.021$.

negative pressure ultrafiltration pump was used to control the input; the replacement rate was 4 L/hour, and the blood flow was kept in 200–300 mL/minute. The treatment lasted 12 hours daily for 1 to 5 days according to the patient's condition.

Detection of the indexes

A total of 5 mL venous blood was extracted from patients before treatment, and at 6, 12, and 24 hours after treatment for 5 days (at 6th day), respectively, and the day of blood collection was uniform for all patients. The levels of PCT, CRP, IL-17, IL-6, and HMGB1 in serum were detected via enzyme-linked immunosorbent assay (ELISA). The PCT kit was provided by Roche, German, and the CRP, IL-17, IL-6, and HMGB1 kits were manufactured by Beckman Coulter Inc., USA. In strict accordance with the instructions of relevant kits, the optical density (OD) value was read at a wavelength of 450 nm using a microplate reader, and the levels of PCT, CRP, IL-17, IL-6, and HMGB1 in corresponding samples were calculated. The serum D-dimer level in patients was detected via immunoturbidimetry, and the relevant kits were supplied by Beckman Coulter Inc., USA.

Evaluation criteria

Criteria for evaluating therapeutic effect [8] were: 1) Cured: within 1 week after treatment the clinical symptoms disappeared with no abnormality in computerized tomography (CT) examination. 2) Markedly effective: within 1 week after treatment most of the clinical symptoms returned to normal and the pathological changes were restored to normal in CT examination. 3) Effective: within 1 week after treatment the clinical symptoms were obviously relieved, and the pathological changes were obviously relieved in CT examination. 4) Ineffective: After 1 week of treatment the clinical symptoms of patients were not obviously improved or aggravated. The total effective rate of treatment=(cured + markedly effective + effective)/total number of cases×100%.

A total of 5 mL venous blood was collected from patients before treatment, and at 6, 12 and 24 hours after treatment. The levels of PCT, CRP, IL-17, IL-6, and HMGB1 in serum were detected via ELISA. The serum D-dimer levels in the 2 groups of patients were detected via immunoturbidimetry.

Statistical analysis

The data were processed by Statistical Product and Service Solutions (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA) software. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and detected by *t*-test. The curative effect was determined by rank sum test. The enumeration data were expressed as rate and detected by χ^2 test. $P < 0.05$ suggested that the difference was statistically significant.

Results

Comparison of curative effects between 2 groups of patients

After 1 week, no mortality had occurred in the 2 groups. The total effective rate of treatment in the observation group (89.13%) was significantly higher than that in the control group (73.91%) ($P < 0.05$) (Table 2).

Comparisons of PCT levels between 2 groups of patients before and after treatment

There were no significant differences in the levels of CRP, IL-17, IL-6, HMGB1, and D-dimer between the 2 groups of patients before and after treatment ($P > 0.05$). The levels of CRP, IL-17, IL-6, HMGB1, and D-dimer in the control group began to decline at 6 hours after treatment, reached the lowest peak at 12 hours after treatment, and recovered at 24 hours after treatment, but all levels were lower than those before treatment ($P < 0.05$). Each index in the observation group showed a continuous downward trend at 6, 12, and 24 hours after treatment, and at different time points after treatment, the indexes were significantly lower than those in the control group ($P < 0.05$) (Tables 3–8).

Discussion

SAP is a clinically common critical disease. Its incidence is increasing every year around the world, and its causes are complex and diverse, including overeating, alcoholism, hypercalcemia, trauma, infections, hyperlipidemia, drug factors, autoimmune diseases, heredity, and other factors [9].

Table 3. Comparisons of PCT levels between two groups of patients before and after treatment (ng/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	2.38±0.78	1.17±0.46*	0.93±0.25*	0.69±0.18*
Control group	46	2.37±0.65	1.95±0.43*	1.37±0.32*	1.62±0.54*
<i>t</i>		0.067	8.401	7.349	11.081
<i>p</i>		0.947	<0.001	<0.001	<0.001

Compared with that before treatment, * *p*<0.05.

Table 4. Comparisons of CRP levels between two groups of patients before and after treatment (mg/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	174.28±9.25	126.38±7.18*	93.23±6.63*	62.38±3.26*
Control group	46	173.84±9.48	148.43±7.42*	114.75±6.82*	138.43±7.52*
<i>t</i>		0.225	14.484	15.345	62.931
<i>p</i>		0.822	<0.001	<0.001	<0.001

Compared with that before treatment, * *p*<0.05.

Table 5. Comparisons of IL-17 levels between two groups of patients before and after treatment (ng/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	12.83±2.23	8.02±0.85*	6.03±0.74*	5.43±0.68*
Control group	46	12.86±2.28	9.94±0.97*	8.32±0.85*	9.07±0.73*
<i>t</i>		0.064	10.097	13.781	24.746
<i>p</i>		0.949	<0.001	<0.001	<0.001

Compared with that before treatment, * *p*<0.05.

Table 6. Comparisons of IL-6 levels between two groups of patients before and after treatment (ng/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	10.68±1.15	7.29±0.63*	6.22±0.65*	5.83±0.54*
Control group	46	10.67±1.18	8.36±0.78*	7.34±0.67*	8.09±0.65*
<i>t</i>		0.041	7.238	8.137	18.139
<i>p</i>		0.967	<0.001	<0.001	<0.001

Compared with that before treatment, * *p*<0.05.

The pathogenesis of SAP is not yet fully understood, although there are a variety of theories such as the inflammatory factor theory, intestinal bacterial translocation theory, microcirculation disorder, trypsin autodigestion theory, and oxidative stress theory [10]. It is generally believed that a large number

of pancreatic enzymes are activated in the patient's body due to various etiological factors, resulting in edema and necrosis of the pancreas and surrounding tissues [11]. At present, the conventional therapy for SAP includes fasting for solids and liquids, gastrointestinal decompression, infection prevention,

Table 7. Comparisons of HMGB1 levels between two groups of patients before and after treatment (µg/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	59.36±3.72	44.52±3.23*	37.98±3.15*	30.84±3.04*
Control group	46	59.47±3.63	51.76±3.47*	40.89±3.27*	45.72±3.35*
<i>t</i>		0.144	10.358	4.347	22.309
<i>p</i>		0.886	<0.001	<0.001	<0.001

Compared with that before treatment, * $p < 0.05$.

Table 8. Comparisons of D-dimer levels between two groups of patients before and after treatment (mg/L).

Group	n	Before treatment	At 6 h after treatment	At 12 h after treatment	At 24 h after treatment
Observation group	46	19.79±3.43	12.27±2.15*	7.84±1.04*	4.43±0.78*
Control group	46	19.82±3.34	16.36±2.27*	11.78±1.35*	12.67±1.26*
<i>t</i>		0.042	8.872	15.681	37.713
<i>p</i>		0.967	<0.001	<0.001	<0.001

Compared with that before treatment, * $p < 0.05$.

inhibition of pancreatic enzyme secretion, maintenance of circulatory balance and stability, and so on. But the effect of conventional therapy has not been good, and it can cause complications with various symptoms, and cause damage to multiple organs [12].

When the intestinal immune barrier of SAP patients is damaged, a large number of bacteria and endotoxins can migrate to the liver, causing liver damage, which makes it is easier to develop high endotoxemia and hyper proinflammatory hypohemia. Pathogenic factors can break through the liver barrier and enter the systemic circulation, causing damage to other tissues and organs. Therefore, comprehensive therapy is usually adopted in the treatment of SAP [13]. With the continuous development of CRTT technology, its functions of regulating water electrolytes, balancing acid-base, and removing metabolic wastes can develop into the functions of protecting endothelial cells, removing inflammatory mediators and endotoxins, regulating immune function of the body and so on. Therefore, CRTT began to be used in the treatment of SAP [14]. The results of our study showed that after 1 week of treatment, the total effective rate of treatment in the observation group was significantly higher than in the control group ($P < 0.05$), indicating that conventional therapy combined with CRTT can speed up the rehabilitation of patients, promptly relieve or alleviate various clinical symptoms, and improve the prognosis.

PCT is an inflammatory factor without hormone activity; it is the most useful biomarker, and it is better than other indicators

for hyper endotoxemia [15]. The release of various inflammatory cytokines in SAP patients will lead to secondary injuries in various tissues and organs. The body will continuously release PCT, thus causing systemic inflammatory response syndrome. CRP is an acute phase reaction protein, for which the detection method is simple and fast, and it is clinically used as a marker to reflect the degree of inflammatory response [16]. IL-17 is a landmark cytokine produced by a subgroup of Th17 cells. When combined with IL-17R, it will activate downstream signaling pathways, participate in inflammatory response, and play an important role in the occurrence and development of inflammation [17]. IL-6, a member of the interleukin family, is a kind of acute phase reactive lymphocyte factor with the 2-way effect of activating the body's defense response and inhibiting the immune function at the same time [18]. The results of our study showed that each index in the observation group showed a continuous downward trend at 6, 12, and 24 hours after treatment, and at different time points after treatment, the indexes were significantly lower than those in the control group ($P < 0.05$). This is because CRRT is more favorable for improving monocyte secretory function, clearing inflammatory mediators, and reconstructing immune balance, and it can remove various inflammatory factors by convection with a relatively fast removal effect. At 24 hours after treatment, the levels of various inflammatory factors can be reduced to a relatively low level, so that the inflammatory state of SAP patients is properly controlled.

HMGB1 was first discovered in the early 1970s as an important late inflammatory mediator widely present in eukaryotic cells. Its name derives from its fast mobility in polyphthalamide gel electrophoresis [19]. When stimulated, dendritic cells, mononuclear macrophages, etc., in SAP patients will produce a large quantity of HMGB1, which is the promoter of late inflammation and can even act as a key factor at the center of inflammation. D-dimer is a degradation product of cross-linked fibrin. When inflammation occurs in SAP patients, it will activate the fibrinolytic system in the body and produce D-dimer, thereby affecting the coagulation function in patients and inducing venous thrombosis [20]. The results of our study showed that each index in the observation group showed a continuous downward trend at 6, 12, and 24 hours after treatment, and at different time points after treatment, the indexes were significantly lower than those in the control group ($P < 0.05$),

indicating that CRRT can quickly and effectively reduce the levels of HMGB1 and D-dimer, and the damage to multiple organs, as well as improve pancreatic microcirculation and correct hypercoagulable state.

Conclusions

The treatment of SAP by CRRT can reduce the release of inflammatory factors and cytokines, and its effect of removing inflammatory factors is more obvious, so it is worthy of clinical promotion and application.

Conflict interest

None.

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