Effects of HV-CRRT on PCT, TNF-α, IL-4, IL-6, IL-8 and IL-10 in patients with pancreatitis complicated by acute renal failure

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Abstract. The aim of the study was to investigate the effects of high-volume continuous renal replacement therapy (HV-CRRT) on procalcitonin (PCT), tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), IL-6, IL-8 and IL-10 in acute pancreatitis complicated by acute renal failure. Eighty-six patients with acute pancreatitis complicated with acute renal failure were selected from September 2014 to September 2016 in our hospital, and were treated by continuous veno-venous hemofiltration (CVVH). The patients were randomly divided into the observation group, treated by the HV-CVVH model with a displacement rate of 4 l/h, and the control group, treated by the normal capacity model with a displacement rate of 2 l/h. The levels of PCT, TNF-α, IL-4, IL-6, IL-8, and IL-10 in serum were measured by ELISA before and 2, 6 and 12 h after treatment, and 12 h after CVVH. The serum PCT and TNF-α levels in the two groups were decreased at 2 h after treatment. The lowest levels appeared at 6 h after treatment, and then recovered, but remained lower than those before treatment ($p<0.05$). The levels of IL-4, IL-6, IL-8 and IL-10, as well as PCT and TNF-α in the two groups were significantly lower than those before treatment, and the decreases in the observation group were more obvious than those in the control group ($p<0.05$). In conclusion, compared with the standard volume method, HV-CRRT can more effectively remove various inflammatory factors and reduce the levels of serum PCT for the treatment of pancreatitis complicated by acute renal failure. Additionally, replacement of the blood filter at appropriate time-points can improve the treatment efficacy.

Introduction

Pancreatitis, one of the most common diseases of the digestive system, is inflammation caused by autodigestion of the pancreas (1). With improvements in living standards and changes in diet, the incidence of pancreatitis is on the increase. The onset and progression of pancreatitis are rapid. Patients with pancreatitis are often accompanied by shock, peritonitis, sepsis, acute renal failure and multiple organ dysfunctions (2). During the pathogenesis of acute pancreatitis, excessive inflammatory mediators are released, which damage distant organs, causing organ dysfunction (3). Acute renal failure refers to continually declining glomerular filtration rate followed by the accumulation of nitrogen waste in the body, which leads to metabolic acidosis, hyperkalemia and acute uremic syndrome. Acute renal failure is one of the main causes of death in patients with pancreatitis (4).

Continuous renal replacement therapy (CRRT) is a new form of renal replacement therapy. CRRT can non-selectively remove endotoxin and inflammatory mediators by dispersion, convection and adsorption, to correct the acid-base balance disorder, adjust immune stability, and maintain stability of the internal environment. CRRT promotes good hemodynamic stability for patients with excessive load and high catabolism, which improves prognosis (5,6). According to different ultrafiltration rates, CRRT is divided as follows: Low capacity <20 ml/(kg·h), standard capacity, 20-34 ml/(kg·h) and high capacity ≥35 ml/(kg·h).

In this study, patients with pancreatitis complicated with acute renal failure were treated with CRRT. Changes in the levels of inflammatory mediators were observed, to provide a theoretical basis for high-volume (HV)-CRRT therapy.

Patients and methods

Patients. Eighty-six patients with acute pancreatitis complicated with acute renal failure were selected in Zengcheng District People's Hospital (Guangdong, China) from September 2014 to September 2016. Inclusion criteria for the study were: i) Patients met the Atlanta diagnostic criteria for acute pancreatitis; ii) clinical manifestations of persistent abdominal pain, breathing difficulty and shock; iii) imaging examination showed pancreatic enlargement and peripancreatic fluid exudation; iv) APACHE II score ≥8 points, serum creatinine increased over 2-fold; and v) patients signed the informed consent. Exclusion criteria for the study were: i) Patients with chronic kidney disease; and ii) patients with pancreatic cancer. The patients were randomly divided into the control and observation groups, with 43 cases each. No significant differences were found in baseline parameters between the two groups ($p>0.05$) (Table I). This study was approved by

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the Ethics Committee of Zengcheng District People's Hospital. Signed written informed consents were obtained from the patients and/or guardians.

Preparation. All the patients were treated with CRRT. The purification equipment was a CRRT machine (model, ADM08/ABM) from Fresenius Medical Care Co. (Dresden, Germany). Before treatment, the catheter and filter were treated with heparin saline (5 mg/l) for 20 min. The right lateral or right femoral vein of the patient was used to indwell a double lumen catheter to establish extracorporeal circulation.

Treatment. Replacement liquid (ingredients: 1.88 mmol/l Ca^{2+}, 2.0 mmol/l K^{+}, 135 mmol/l Na^{+}, 0.75 mmol/l Mg^{2+}, 108 mmol/l Cl^{-}, 33.75 mmol/l lactate and 1.5 g/l glucose; Shanghai Changzheng Pharmaceutical Factory) was diluted, and input with a negative pressure ultrafiltration pump. Patients in the control group were treated with CRRT, and the ultrafiltration rate was 20 ml/(kg·h). Patients in the observation group were treated with HV-CRRT and the ultrafiltration rate was 35 ml/(kg·h). Low molecular weight heparin (SFDA approval no. H20020469; Tianjin Hongri Pharmaceutical Co., Ltd., Tianjin, China) was used for anticoagulation with an initial dose of 3,000 units, and subsequent doses of 500 U/h. The dose was reduced for patients with bleeding tendency. The trail and filters were rinsed with 200 ml of sodium chloride solution every hour. When using the HV-continuous veno-venous hemofiltration (CVVH) mode, blood flow was maintained at 200-300 ml/min. The patients were treated for 12 h/day for 1-5 days according to the patient's condition.

Observational indicators. Arterial blood (5 ml) was extracted from patients before treatment; at 2, 6 and 12 h after treatment; and 12 h after CVVH. The levels of procalcitonin (PCT), tumor necrosis factor-α (TNF-α), interleukin 4 (IL-4), IL-6, IL-8 and IL-10 in serum were measured by ELISA. The PCT kit was purchased from Roche (Mannheim, Germany). TNF-α, IL-4, IL-6, IL-8 and IL-10 kits were all purchased from Beckman Coulter (Brea, CA, USA). All the procedures were performed according to the manufacturer's instructions. The OD values were read by a microplate reader (wavelength, 450 nm), and the corresponding concentrations of PCT, TNF-α, IL-4, IL-6, IL-8 and IL-10 were calculated and recorded.

Statistical analysis. Data were processed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) statistical software. Numerical data are presented as mean ± standard deviation (mean ± SD) and a t-test was used for comparisons between groups. Quantitative data are presented as rate, and a χ^2 test was used for comparisons between groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of the levels of PCT before and after treatment in the two groups. The serum levels of PCT were decreased in the two groups at 2 h after treatment, and were lowest at 6 h after treatment (0.93±0.23 and 1.35±0.32 ng/l, respectively) and then recovered. However, the levels remained lower than those before treatment (p<0.05), and the decrease in the levels of PCT was more obvious in the observation group than in the control group (p<0.05) (Table II).

Table I. Baseline parameters of patients.

Items	Observation group (n=43)	Control group n=43	t/χ^2	P-value
Sex (male/female)	22/21	20/23	0.046	0.829
Age (years)	40-80	40-85		
Average age (years)	38.34±5.47	39.15±5.56	0.681	0.497
MAP (mmHg)	98.57±13.92	97.68±13.74	0.298	0.766
WBC (10^9/l)	16.32±5.73	15.74±5.38	0.484	0.629
Body temperature (˚C)	38.35±0.87	38.14±0.78	1.179	0.242
Cause of disease (n,%)				
Hyperlipidemia	19 (44.18)	17 (39.53)	0.047	0.827
Alcoholism	15 (34.88)	13 (30.23)	0.053	0.818
Cholelithiasis	7 (16.27)	9 (20.93)	0.076	0.781
Other	2 (4.65)	4 (9.30)	0.179	0.672
APACHE II score before treatment	18.75±3.14	18.98±3.26	0.315	0.739
Serum BUN (mmol/l)	27.93±7.83	27.14±7.35	0.482	0.631
FiO_2/O_2 (mmHg)	153.34±8.83	152.75±7.15	0.341	0.734

MAP, mean artery pressure; WBC, white blood cell; APACHE, Acute Physiology and Chronic Health Evaluation; BUN, blood urea nitrogen; FiO_2, fraction of inspiration O_2.

Comparison of TNF-α levels before and after treatment in the two groups. The serum TNF-α levels in the two groups at 2, 6 and 12 h after treatment were lower than those before treatment. The lowest levels appeared at 6 h after treatment (60.23±6.63 and 64.75±6.82 ng/l, respectively), and then recovered slightly at 12 h after CVVH. However, the levels remained lower than those before treatment (p<0.05), and the levels of TNF-α at the different time-points after treatment in the observation group were significantly lower than those of the control group (p<0.05) (Table III).

Comparison of IL-4 levels before and after treatment in the two groups. The levels of IL-4 in the two groups were significantly lower than those before treatment, and the decreases in the observation group were more obvious than those in the control group (p<0.05) (Table IV).

Comparison of IL-6 levels before and after treatment in the two groups. The levels of IL-6 in the two groups were significantly lower than those before treatment, and the decreases in the observation group were more obvious than those in the control group (p<0.05) (Table V).

Comparison of IL-8 levels before and after treatment in the two groups. The levels of IL-8 in the two groups were significantly lower than those before treatment, and the decreases in the observation group were more obvious than those in the control group (p<0.05) (Table VI).

Table II. Comparison of PCT levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	2.28±0.75	1.78±0.48	0.93±0.23	1.29±0.48	1.71±0.53	37.821	<0.001
Control	2.27±0.68	1.98±0.42	1.35±0.32	1.63±0.59	1.97±0.62	25.415	<0.001
t	0.065	4.192	6.989666	2.931	2.090		
P-value	0.948	0.042	<0.001	0.004	0.039		

PCT, procalcitonin.

Table III. Comparison of TNF-α levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	74.28±9.25	65.38±7.18	60.23±6.63	63.38±7.26	64.23±8.65	67.342	<0.001
Control	73.84±9.48	69.43±7.42	64.75±6.82	67.43±7.52	68.75±8.76	39.452	<0.001
t	0.218	2.572	3.116	2.541	2.408		
P-value	0.828	0.012	0.002	0.012	0.018		

TNF-α, tumor necrosis factor-α.

Table IV. Comparison of IL-4 levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	146.43±12.24	129.67±9.23	116.35±7.25	128.67±8.23	136.25±8.27	71.78	<0.001
Control	147.62±12.58	137.27±9.64	126.45±7.32	136.82±8.79	139.47±6.21	56.39	<0.001
t	0.445	3.734	6.428	4.438	2.042		
P-value	0.657	<0.001	<0.001	<0.001	0.044		

IL-4, interleukin-4.

Table V. Comparison of IL-6 levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	168.78±11.56	154.68±9.53	143.36±8.47	153.64±8.13	156.52±8.37	93.57	<0.001
Control	169.44±11.34	160.63±9.74	154.75±8.26	160.64±8.25	161.73±9.45	89.46	<0.001
t	0.267	2.863	6.313	3.963	2.706		
P-value	0.790	0.005	<0.001	<0.001	0.008		

IL-6, interleukin-6.

Comparison of IL-10 levels before and after treatment in the two groups. The levels of IL-l0 in the two groups were significantly lower than those before treatment, and the decreases in the observation group were more obvious than those in the control group ($p<0.05$) (Table VII).

Discussion

Overview of pancreatitis. Acute pancreatitis is caused by chemical inflammation of the pancreas induced by digestive enzymes. The incidence of acute pancreatitis is increasing worldwide (2). Pancreatitis is caused by various factors, including alcoholism, overeating, abdominal trauma, hyperlipidemia, intestinal bacterial translocation, drug factors, pancreatic duct obstruction and genetic factors, which can cause the activation of trypsin, leading to edema and necrosis of the pancreas and surrounding tissues (7,8). There are various treatment methods including gastrointestinal decompression, prohibiting food and water, prevention of infection, maintenance of circulation balance, and inhibition of pancreatic secretion (9). However, the outcomes of these methods were proven to be poor. Pancreatitis is usually complicated with various other diseases, such as systemic inflammatory response syndrome and compensatory anti-inflammatory

Table VI. Comparison of IL-8 levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	362.48±21.27	314.64±16.58	276.35±9.25	284.67±9.26	306.54±9.26	79.46	<0.001
Control	363.43±21.25	332.65±17.28	298.35±9.25	304.67±9.76	336.48±10.25	85.74	<0.001
t	0.207	4.932	11.028	9.748	14.213		
P-value	0.837	0.005	<0.001	<0.001	<0.001		

IL-8, interleukin-8.

Table VII. Comparison of IL-8 levels before and after treatment in the two groups (ng/l).

Groups	Before treatment	2 h after treatment	6 h after treatment	12 h after treatment	12 h after CVVH	F	P-value
Observation	147.43±9.57	121.67±7.23	114.35±7.25	116.67±6.58	125.35±6.25	76.38	<0.001
Control	148.15±9.78	130.54±7.38	123.45±7.75	125.67±7.23	130.15±7.36	83.75	<0.001
t	0.345	5.630	5.623	6.037	3.260		
P-value	0.731	<0.001	<0.001	<0.001	0.002		

IL-8, interleukin-8.

response syndrome. These two syndromes can occur sequentially or simultaneously, leading to damage of multiple organs. Decreased urine volume, persistent oliguria and increased serum creatinine occur in patients with pancreatitis. Although this renal function injury is reversible, it can reduce the body's response to external factors, seriously affecting the prognosis of patients (9,10).

Clinical application of CRRT. CRRT was first applied for the clinical treatment of simple renal failure in the 1970s. With the application of comprehensive treatment for acute pancreatitis, CRRT began to be used in patients with pancreatitis combined with acute renal failure. With the continuous development of CRRT technology, new functions of CRRT besides water and electrolyte regulation, acid and alkali balance maintenance, and metabolic waste removal have been developed. These functions include immune function regulation, endothelial cell protection, removal of inflammatory mediators and endotoxin, maintenance of cardiovascular stability, and body temperature regulation (11,12). CRRT plays a role in functional support of the impaired kidney in severe pancreatitis patients with acute renal failure, and provides life support for these patients (13). Determining the therapeutic dose of CRRT is an area of intense clinical research. According to the ultrafiltration rate and liquid displacement volume, the model can be divided into 4 modes: Low capacity <20 ml/(kg·h), standard capacity, 20-34 ml/(kg·h), high capacity, 35-50 ml/(kg·h) and ultra-high capacity >50 ml/(kg·h). At present, the optimal dose remains uncertain. Studies have shown that HV-CRRT may be more beneficial for improvement of mononuclear cell secretion, clearance of inflammatory mediators and immune balance reconstruction. However, fast drug metabolism, nutrient loss, coagulation system activation and other risks still exist (14).

Effects of CRRT on serum PCT, TNF-α, IL-4, IL-6, IL-8 and IL-10. PCT is a hormone-free inflammatory factor with a half-life of approximately 24 h (15). Previous findings have shown that compared with other markers, PCT is the most useful biomarker for the diagnosis of sepsis (16). PCT can be induced during the acute inflammatory response, which in turn increases damage to the body caused by bacterial infection, leading to secondary renal injury (17). Our study showed that serum PCT levels were decreased at 2 h after treatment. The lowest levels appeared at 6 h after treatment (0.93±0.23 and 1.35±0.32 ng/l, respectively), and then recovered. This was because the adsorption was saturated, and the PCT clearance ability was reduced. However, the PCT levels remained lower than those before treatment.

TNF-α is a mononuclear inflammatory cytokine that plays an important role in the acute inflammatory response in patients with pancreatitis (18). Our study showed that serum TNF-α levels in the two groups at 2, 6 and 12 h after treatment were lower than those before treatment ($p<0.05$), and the lowest levels appeared at 6 h after treatment (0.93±0.23 and 1.35±0.32 ng/l, respectively). In addition, TNF-α was lower in the observation group than in the control group. This was because CRRT can remove TNF-α by convective clearance, and the increased ultrafiltration rate can increase the effect of removal. The mechanism of HV-CRRT is that increased blood flow can increase the amount of TNF-α going through the filter per unit time. Therefore, the convective clearance is also increased. In addition, the solute is more likely to enter the deep layer of the membrane, so that the effective adsorption area of the synthetic membrane becomes larger. The levels of TNF-α recovered slightly at 12 h after CVVH, but remained lower than those before treatment.

IL-4, IL-6, IL-8 and IL-10 have various functions in immune responses and apoptosis in patients with pancreatitis complicated with acute renal failure. These factors can both mobilize the defensive response and inhibit immune function (19). In the early stage, these factors can lead to the occurrence of compensatory anti-inflammatory response

syndrome. These factors can interact with each other to amplify the inflammatory response to accelerate the progression of renal failure (20). We found that the levels of IL-4, IL-6, IL-8 and IL-10 were significantly lower in the two groups compared with those before treatment, and the decreases in the observation group were more obvious than those in the control group ($p<0.05$). These inflammatory factors can be removed by convection clearance. The clearance was most obvious in the early stage of treatment (2 h). When adsorption efficiency reached saturation, the clearance rate decreased.

In conclusion, compared with the normal dose mode CRRT treatment, the efficiency of inflammatory factor clearance of HV-CRRT is significantly higher in the treatment of patients with pancreatitis with acute renal failure. It should therefore be employed in the clinic.

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