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Original Article

Effect of continuous renal replacement therapy adjuvant to broad-spectrum enzyme inhibitors on the efficacy and inflammatory cytokines in patients with severe acute pancreatitis

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Abstract: Objective: To investigate the effect of continuous renal replacement therapy (CRRT) combined with ulinastatin, a broad-spectrum enzyme inhibitor, on the treatment effect and inflammatory mediator levels in patients with severe acute pancreatitis (SAP). Methods: A total of 80 patients with SAP admitted to our hospital were divided into two groups according to a random number table, with 40 cases in the control group and 40 cases in the experimental group. The control group was treated with the broad-spectrum enzyme inhibitor ulinastatin, and the experimental group was treated with continuous renal replacement therapy (CRRT) in addition to the control group's treatment method. The clinical efficacy was evaluated. Serum inflammation indicators, critical illness-related scores, pancreatic microcirculation and coagulation indicators were also detected before and after treatment. Results: After 14 days of continuous intervention, the total effective rate of the experimental group was 92.50%, and that of the control group was 75.00%, with statistical significance between the two groups ($P<0.05$). The expression of APN in the two groups' serum increased, and the other inflammatory indexes decreased. The experimental group's serum APN was higher than that of the control group, and the other inflammatory indexes were lower than those of the control group (all $P<0.001$). The two groups' critical illness-related scores were improved, and there was a difference between the two groups ($P<0.05$). The levels of BF and BV increased, while TTP levels decreased, and there was a difference between the experimental and control groups (all $P<0.01$). The coagulation indexes of the two groups of patients were all improved. Compared with the control group, the coagulation indexes of the experimental group were lower. There was a difference between the two groups ($P<0.01$). Conclusion: CRRT adjuvant to broad-spectrum enzyme inhibitor ulinastatin can significantly improve the inflammatory response, microcirculation, hypercoagulability and clinical treatment efficacy in patients with severe acute pancreatitis.

Keywords: Severe acute pancreatitis, CRRT, ulinastatin, inflammatory cytokines, coagulation index, pancreatic microcirculation, critical illness score

Introduction

Acute pancreatitis (AP) is a local or systemic inflammatory response caused by the excessive activation of pancreatic enzymes [1]. Severe acute pancreatitis (SAP) is a particular type of AP. According to epidemiology, the annual incidence of SAP accounts for 10% to 20% of AP, and the incidence rate is increasing annually. The mortality rate is as high as 17%. The pathogenic factors are related to bile duct diseases, alcoholism, and binge eating [2]. SAP is an acute inflammatory response. Pancreatic protease activation can recruit and release inflammatory mediators. A severe inflammatory response can aggravate overcompensation and the response of the immune system and increase systemic infection risk. Inflammatory cytokines play a role in promoting the occurrence and development of SAP. Tumor necrosis factor-α (TNF-α) participates in the activation of NK and T lymphocytes. Immunohistochemical results show that TNF-α expression in the pancreatic tissues of patients with SAP increased, and that blocking TNF-α expression could alleviate the disease [3].

At present, internal medicine intervention for SAP diseases has been widely recognized in clinical practice [4]. Ulinastatin is a glycoprotein extracted from male urine, rich in multiple amino acids. It is non-immunogenic and safe [5]. Continuous renal replacement therapy (CRRT) is a standard method for treating critical diseases. Continuous blood filtration is performed on SAP patients according to the principle of glomerular filtration [6]. However, at present, there is little literature about the use of CRRT assisted with ulinastatin, a broad-spectrum enzyme inhibitor, to improve SAP. Therefore, this study investigates CRRT combined with ulinastatin in the treatment of SAP as an innovative point, observes and analyzes the effect of the above-combined therapy on the patient's efficacy, inflammatory factors, severity score and coagulation function.

Materials and methods

General information

In this prospective study, a total of 80 patients with SAP admitted to our hospital from October 2016 to November 2020 were selected as the research subjects.

Inclusive criteria: (1) patients who were older than 18 years old; (2) patients whose symptoms were compliant with the 2013 guidelines for diagnosis and treatment of AP [7]; (3) patients who had acute and continuous abdominal pain; (4) patients whose Chronic Health Evaluation (APACHE) II >8 points [8]; (5) CT detection grades were D (peripancreatic exudation) and E (pancreatic necrosis and abscess).

Exclusion criteria: (1) patients with digestive system diseases caused by other inducements; (2) patients with AP caused by biliary system diseases; (3) patients with severe heart, liver and kidney disorders; (4) patients with respiratory dysfunction and cancer; (5) patients with language disorders and mental illnesses; (6) pregnant or lactating women; (7) patients who have participated in other clinical projects.

Patients were randomly divided into the control and experimental groups, with 40 cases in each group. The control group patients were treated with ulinastatin, a broad-spectrum enzyme inhibitor, while the patients in the experimental group were treated with CRRT combined with ulinastatin. Our hospital Ethics Committee approved this study with the informed consent from the patients and their families.

Methods

All patients received primary treatment after admission, including continuous nutritional support by nasal feeding, a gastrointestinal examination with water fasting, inhibition of gastric acid secretion by omeprazole, reduction of pancreatic secretion by intravenous infusion of somatostatin, correction of electrolytes and maintenance of acid-base balance, prevention of infection by ceftriaxone, analgesia by dezocine, prevention of thrombosis by low molecular weight heparin calcium, etc.

The control group was treated with ulinastatin (Guangdong Tianpu Biochemical Medicine Co., Ltd., China). A total of 100,000 units of ulinastatin were dissolved in 50 mL 0.9% sodium chloride solution and were given an intravenous injection for eight hours each time. The experimental group was treated with CRRT based on the previous treatment scheme. Equipment used for CRRT was purchased from Guangzhou guangdechang Technology Co., Ltd., including the continuous blood purification system, polysulfone membrane dialyzer and disposable Extracorporeal Blood Circuit. The total membrane area was 1.8 m^2. The dosage of heparin and its antagonist protamine was precisely calculated to maintain APTT within a normal range. The APTT was controlled at 40-80 s and the filter was replaced four times per hour. The CVVH mode was used for treatment. The blood circulation volume was 200 mL/h and the total replacement volume was 2500-3000 mL/h. The single CRRT treatment time was (12.8±8.0) h. Both groups were treated continuously for 14 days.

Outcome measures

Primary outcome measures

Clinical efficacy of the two groups of patients: The clinical efficacy indicators include the disappearance of gastrointestinal symptoms such as abdominal pain and bloating, the recovery of whole blood cells and blood amylase levels, and the liver and kidney function recovery [8]. The effect standard is divided into cured, markedly effective, effective and ineffective. Total

Table 1. Efficacy criteria

Standard	
Get well	Clinical symptoms, gastrointestinal symptoms and laboratory indicators all meet the above standards within 5 days
Markedly effective	Clinical symptoms, gastrointestinal symptoms and laboratory indicators all meet the above standards within 7 days
Effective	Clinical symptoms, gastrointestinal symptoms and laboratory indicators all meet the above standards within 10 days
Ineffective	All clinical symptoms, gastrointestinal symptoms and laboratory indicators have not met the above standards within 10 days

effective rate = Number of cases of (cured + markedly effective)/Total number of cases. See **Table 1**.

Serum inflammatory indicators of the two groups of patients: When the patient was fasting, 3 mL peripheral blood from the elbow was collected. The TGL-15M desk micro high-speed freezing centrifuge purchased from Hunan Pingfan Technology Co., Ltd., was used to separate 3 mL of peripheral blood at 3000 r/min for 10 min. The serum was reserved. C-reactive protein (CRP) was detected by immunoturbidimetry. TNF-α, IL-6 and adiponectin (APN) were detected by ELISA. All the kits were purchased from Nanjing Shanben biology Co., Ltd.

Critical illness-related scores of the two groups of patients: The APACHE II score could be evaluated according to patients' heart rate, blood pressure, pH, age and chronic health status [9]. Physiological indicators included heart rate, blood pressure and pH. Chronic health status was assessed by two factors, which were health status and postoperative complications. The score ranged from 0 to 71 points. The higher the score, the more serious the disease.

Balthazar CT Score was mainly used for disease grading and evaluating the degree of pancreatic necrosis [9]. Disease grading: 0 points: no inflammation and normal peri-glandular area; 1 point: diffuse enlargement of the gland; 2 points: inflammation with mild exudation; 3 points: obvious exudation; 4 points: pancreatic abscess and fat necrosis. Necrosis degree: 0 points: no necrosis; 2 points: necrosis degree <30%; 4 points: necrosis degree 30%-50%; 6 points: necrosis degree >50%. The higher the score, the more severe the pancreatic injury.

MODS score was used for evaluating the function of patients' lung, kidney, liver, cardiovascular system, nervous system and hematology [10]. A 5-point system was adopted, with 0 points representing the normal state and 1-4 points representing organ abnormalities. The highest score is 24 points. The higher the score, the more significant the organ abnormalities.

Secondary outcome measures

Indicators of pancreatic microcirculation in the two groups of patients: Before and after the treatment, Lonwin's 16-slice CT scanned the patients' pancreas, with a layer distance of 5 cm and a layer thickness of 5 cm. The number was processed by a workstation. Two radiologists who have worked for more than five years interpreted the results and recorded the blood flow (BF), blood flow volume (BV) and perfusion peak time (TTP).

Comparison of coagulation function between the two groups: The blood was collected and separated according to the guidance mentioned above. The CS-5100 automatic coagulation analyzer and the supporting equipment were purchased from Dacheng Medical Equipment Company that were used for detection. The serum lipase (LPS) and amylase (AMY) content were detected by the rate method, and the D-Dimer (D-D) level was detected by the latex agglutination method. The steps were strictly performed following the instructions.

Statistical analysis

SPSS 23.0 software was used to analyze the data. The measurement data of inflammation, critical illness score, microcirculation and coagulation function were expressed as ($\bar{x} \pm sd$) and analyzed by t-test. The count data were represented as n (%) and analyzed by the χ^2 test. $P<0.05$ indicated that the difference was significant.

Results

Comparison of the baseline data between the two groups

There was no significant difference in gender, average age, average course of the disease,

Table 2. General information of the two groups of patients

Group	Control group (n=40)	Test group (n=40)	χ^2/t	*P* value
Gender (n)			0.457	0.796
Male	24	21		
Female	16	19		
Average age (years)	50.0±6.3	49.5±6.6	0.763	0.448
Average course of disease (h)	10.6±2.1	10.2±1.9	1.340	0.184
BMI (kg/m^2)	23.71±1.03	24.01±1.01	1.359	0.178
Cause (n)			0.492	0.921
Biliary disease	17	19		
Alcoholism	11	10		
Overeating	10	10		
Unknown reason	2	1		
Underlying disease (n)			0.354	0.950
Diabetes	6	7		
Hypertension	4	5		
Coronary heart disease	3	2		
Acute respiratory distress syndrome	1	1		

Note: BMI: Body Mass Index.

Table 3. Comparison of the total clinical effective rate of the two groups of patients

Group	n	get well	Markedly effective	effective	Ineffective	Total effective rate (%)
Control group	40	21	9	8	2	30 (75.00)
Test group	40	27	10	2	1	37 (92.50)
t						11.251
P value						0.001

BMI, etiology and complicated underlying disorders between the two groups (all P>0.05). See **Table 2**.

Comparison of total clinical efficacy rate between the two groups

After 14 days of continuous intervention, the experimental group's total efficacy rate was 92.50%, and that of the control group was 75.00%, with statistical significance between the two groups (P<0.05). See **Table 3**.

Comparison of serum inflammatory indicators between the two groups before and after treatment

Before the intervention, there was no significant difference in the serum levels of CRP, TNF-α, IL-6 and APN in all SAP patients (all P>0.05). After the intervention, the serum APN expression in the two groups increased, and the other inflammatory indexes decreased. The serum APN in the experimental group was higher than that in the control group, while the other inflammatory indexes were lower than those in the control group (all P<0.001). See **Table 4**.

Comparison of critical illness-related scores between two groups before and after treatment

Before the intervention, there was no significant difference in the APACHE II score, Balthazar CT Score and MODS between the two groups (all P>0.05). After the intervention, the two groups' critical illness-related scores improved, and those in the experimental group were lower than those in the control group. There were differences between the two groups (all P<0.01). See **Table 5** and **Figure 1**.

Comparison of pancreatic microcirculation indexes between the two groups before and after treatment

Before the intervention, the BF, BV and TTP levels between the two groups were not statisti-

Table 4. Comparison of serum inflammation index levels before and after treatment in the two groups

Factors	Control group (n=40)	Test group (n=40)	t	*P* value
CRP (mg/L)				
Before treatment	195.30±18.14	197.02±16.27	0.446	0.657
After treatment	22.04±3.32	12.17±1.50	17.130	<0.001
t	59.420	71.550		
P value	<0.001	<0.001		
TNF-α (pg/L)				
Before treatment	36.14±5.06	35.84±5.51	0.254	0.800
After treatment	18.22±1.96	13.04±1.47	13.270	<0.001
t	20.890	25.250		
P value	<0.001	<0.001		
IL-6 (pg/L)				
Before treatment	77.45±6.88	76.80±7.01	0.419	0.677
After treatment	43.17±6.01	29.55±4.66	11.330	<0.001
t	23.730	35.500		
P value	<0.001	<0.001		
APN (mg/L)				
Before treatment	16.22±3.31	16.05±2.33	0.267	0.791
After treatment	20.17±3.69	25.80±3.50	7.001	<0.001
t	5.040	14.670		
P value	<0.001	<0.001		

Note: CRP: C-reactive protein; TNF-α: tumor necrosis factor; IL-6: interleukin-6; APN: adiponectin.

Table 5. Comparison of critical illness-related scores between the two groups before and after treatment

Factors	Control group (n=40)	Test group (n=40)	t	*P* value
APACHE II scores				
Before treatment	15.50±4.60	15.00±5.10	0.465	0.643
After treatment	10.50±3.50	7.60±2.20	4.437	0.001
t	5.471	8.568		
P value	<0.001	<0.001		
Balthazar CT scores				
Before treatment	6.49±1.15	6.61±1.09	0.479	0.633
After treatment	5.63±0.90	3.82±0.46	11.330	<0.001
t	3.725	14.910		
P value	0.001	<0.001		
MODS scores				
Before treatment	7.25±2.16	7.14±2.38	0.217	0.829
After treatment	5.01±1.67	3.74±1.05	4.072	0.001
t	5.189	8.266		
P value	<0.001	<0.001		

Note: APACHE II: Chronic Health Assessment System II; Balthazar CT: CT severity index of acute pancreatitis; MODS: multiple organ dysfunction syndrome score.

cally significant (all P>0.05). After the intervention, the BF and BV levels increased, while the TTP level decreased. The comparison between the two groups was statistically significant (all P<0.01). See **Table 6** and **Figure 2**.

Comparison of the coagulation indexes between the two groups before and after treatment

Before the intervention, there was no significant difference in the LPS, AMY and D-D levels between the two groups (all P>0.05). After the intervention, the coagulation indexes were improved. Compared with the control group, the experimental group's coagulation index expression level was lower, and there was statistical significance between the two groups (P<0.01). See **Table 7**.

Discussion

SAP is a kind of critical disease. Although the clinical treatment plan is constantly improved, the mortality rate is still as high as 35% [11]. At present, comprehensive therapy such as analgesia and anti-inflammation is used in the treatment of SAP. This study investigates the effect of CRRT combined with ulinastatin on the clinical efficacy and inflammatory cells in patients with SAP.

Ulinastatin is a non-toxic exogenous protease inhibitor from the human body. It has strong antiprotease activity and can block the release of inflammatory factors to protect the organs [12, 13]. CRRT can be a slow and continuous treatment method. Through the adsorption and convection of the filter membrane, harmful substances in the blood

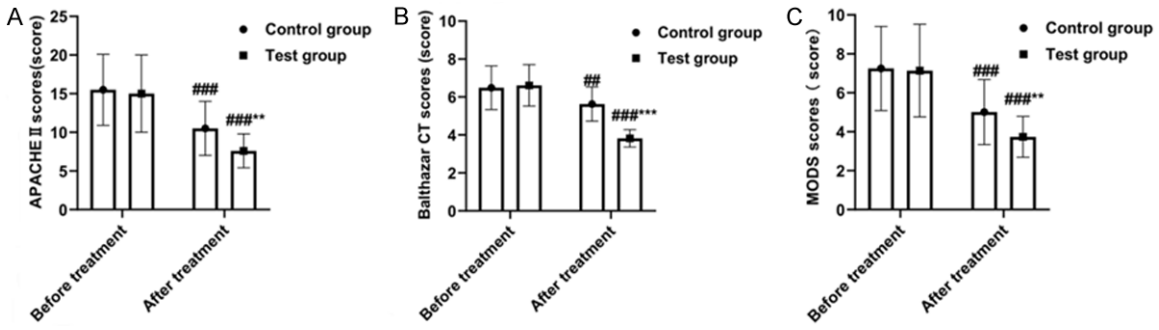

Figure 1. Critical illness-related scores before and after the treatment. A: APACHE II scores; B: Balthazar CT scores; C: MODS scores. Compared with those before treatment, ##P<0.01, ###P<0.001; compared with the control group, **P<0.01, ***P<0.001. APACHE II: Chronic Health Assessment System II; Balthazar CT: CT severity index of acute pancreatitis; MODS: multiple organ dysfunction syndrome score.

Table 6. Comparison of pancreatic microcirculation indexes before and after treatment in the two groups

Factors	Control group (n=40)	Test group (n=40)	t	*P* value
BF (mL·g^{-1}·min^{-1})				
Before treatment	510.30±74.15	506.91±80.55	0.196	0.643
After treatment	652.70±95.05	784.20±96.63	6.136	<0.001
t	7.471	13.940		
P value	<0.001	<0.001		
BV (mL/100 mL)				
Before treatment	76.01±9.68	75.80±10.20	0.095	0.925
After treatment	94.11±11.33	104.49±12.30	3.926	<0.001
t	7.682	7.596		
P value	0.001	<0.001		
TTP (0.1 s)				
Before treatment	191.20±25.50	189.60±27.00	0.272	0.786
After treatment	140.20±16.62	126.30±12.41	4.238	<0.001
t	10.600	13.470		
P value	<0.001	<0.001		

Note: BF: blood flow; BV: blood flow volume; TTP: perfusion peak time.

can be removed and the inflammatory mediators can be better eliminated at the same time to improve pancreatic inflammation. This study confirmed that the total effective rate of the treatment in the experimental group was higher than that of the control group, indicating that the combination of the two can improve the treatment effect by reducing patients' persistent pain. Zhao et al. confirmed that ulinastatin combined with CRRT could significantly improve the clinical efficacy of SAP patients and accelerate the rehabilitation process, which is similar to the results of this study [14].

Excessive activation of inflammatory cytokines will release other inflammatory mediators into the blood, produce many oxygen free radicals and aggravate the cascade reaction of inflammatory cytokines, leading to pancreatic dysfunction in SAP patients. The disordered function of the pancreas induces a systemic inflammatory response, leading to organ failure and death. Inflammatory factors such as CRP, TNF-α and IL-6/8 play an important role in the above process [15]. Therefore, reducing the cascade of inflammatory factors in the peripheral blood is critical in alleviating SAP. This study confirmed that the expression of serum inflammatory factors in the experimental group was lower than that in the control group, indicating that ulinastatin combined with CRRT is beneficial to inhibit the expression of inflammatory factors and improve the patient's condition. Ulinastatin can play the role of immune regulation in SAP patients. It may improve the balance of Th17 and Treg cells, enhance interleukin release by Th17 and improve oxidative stress and inflammatory damage in SAP patients. Wu T J et al. confirmed that ulinastatin could stabilize the lysosomal membrane and reduce the excessive secretion of inflammatory factors in septic patients with inflammatory injury, thereby improving the patient's condition [16]. CRRT functions in SAP patients by inhibiting the inflammatory cascade reaction by adsorption and convection, removing various enzymes and endotoxin, improving circulation, re-adjust-

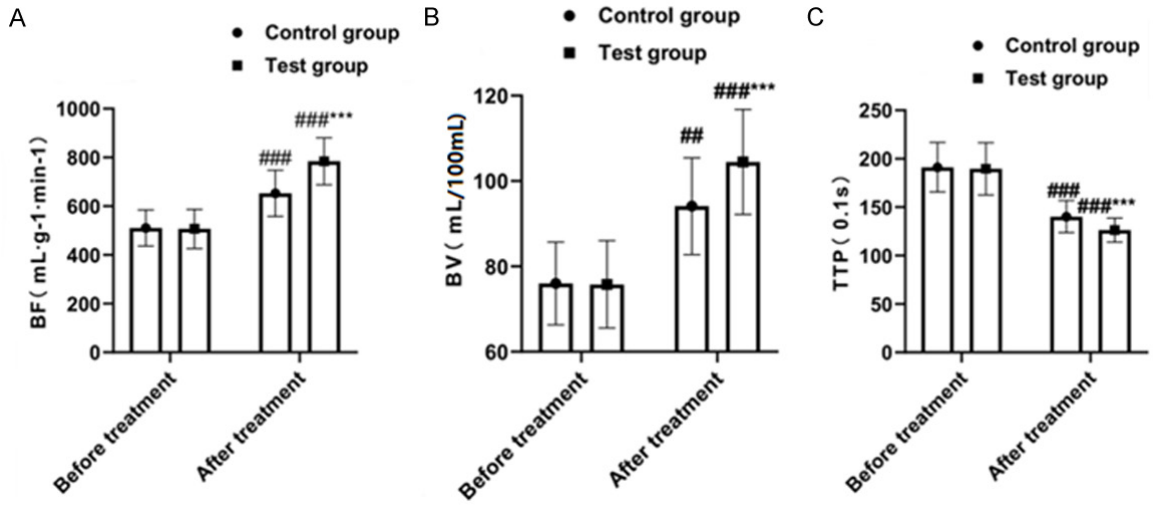

Figure 2. Comparison of pancreatic microcirculation indexes between the two groups. A: BF; B: BV; C: TTP. Compared with those before treatment, ##P<0.01, ###P<0.001; compared the control group, ***P<0.001. BF: blood flow; BV: blood flow volume; TTP: perfusion peak time.

Table 7. Comparison of coagulation indexes before and after treatment in the two groups

Factors	Control group (n=40)	Test group (n=40)	t	*P* value
LPS (U/L)				
Before treatment	1262.08±115.10	1266.20±114.30	0.220	0.873
After treatment	363.25±56.20	156.58±20.15	21.890	<0.001
t	44.380	60.470		
P value	<0.001	<0.001		
AMY (U/L)				
Before treatment	790.14±95.30	788.52±96.38	0.076	0.925
After treatment	255.20±45.61	102.05±12.36	20.500	<0.001
t	32.020	44.680		
P value	0.001	<0.001		
D-D (μg/mL)				
Before treatment	2.80±1.31	2.72±1.26	0.287	0.781
After treatment	1.15±0.90	0.62±0.10	3.702	0.001
t	6.566	10.510		
P value	<0.001	<0.001		

Note: LPS: serum lipase; AMY: amylase; D-D: D-dimer.

ing the body's immune function, and maintaining internal environment stability [17].

At present, the APACHE score which can better reflect the severity of SAP is widely used in ICU patients [18]. With the development of imaging technology, the Balthazar CT score plays an important role in the diagnosis, severity evaluation and local complication evaluation of SAP. The MODS score can better reflect the degree of damage to the body's major organs, and can act as an indicator to evaluate the prognosis of patients. This study showed that the experimental group's critical illness-related score was lower than that of the control group, indicating that ulinastatin combined with CRRT could reduce the critical illness-related score by improving the patient's condition. Endogenous Ulinastatin content is not enough to resist inflammatory damage in critically ill SAP patients. Exogenous increase of ulinastatin can reduce TNF-α translation and secretion by inhibiting the transcription of various factors such as NF-KB. It can protect the body from inflammatory damage and improve the critical state. The mechanism by which CRRT therapy can reduce the critical illness score of SAP patients may lie in the long-term elimination of inflammation and toxins in the blood, continuous immune balance and improvement of the body's ability to resist inflammation. Kang et al. confirmed that ulinastatin combined with CRRT can effectively improve the clinical efficacy of patients with mul-

tiple organ dysfunction and reduce ICU mortality [19].

Pancreatic microcirculation disorders play an important role in the pathogenesis of SAP. Pancreatic microcirculation disorders in the early stage of SAP are related to peripheral circulation ischemia. Circulatory disorders can lead to spasms and contraction of arterioles, induce thrombosis and affect hemorheology. The body's microcirculation and coagulation function influence each other. Coagulation dysfunction is one of the important mechanisms in the development of SAP. Ulinastatin improves the microcirculation function of SAP patients mainly by up-regulating the content of pancreatic kininogenase. The combination of pancreatic kininogenase and the receptor can produce prostacyclin that will dilate blood vessels, further increase the blood flow in blood vessels and improve microcirculation. Ulinastatin has a protective effect on platelets. This kind of protective effect may be related to the inhibition of plasmin and the reduction of platelet activity, which is conducive to ensuring the functional integrity of vascular endothelial cells. CRRT can improve the blood microcirculation of SAP patients by eliminating harmful substances, accelerating the body's metabolism, providing the steady-state balance of water and electrolytes, controlling the systemic inflammatory response, and protecting the function of vascular endothelial cells and organs. Zhang et al. said that ulinastatin reduced the microcirculation disorders of SAP patients mainly by reducing the level of inflammatory factors and restoring the coagulation function [20]. Zhen et al. confirmed that CRRT can ensure the recovery of microcirculation by improving the infection status of SAP patients, which is similar to the results of this paper [21].

Due to the time issue, the small sample size included in this study may impact the expected results. Later, we will work with other research groups to further explore the effect of CRRT assisted broad-spectrum enzyme inhibitors on SAP disease and its mechanism of action through animal experiments, to provide a practical basis for the clinical treatment of SAP patients.

In conclusion: CRRT combined with ulinastatin can significantly improve the inflammatory response, microcirculation, hypercoagulability and clinical efficacy in patients with severe acute pancreatitis.

Disclosure of conflict of interest

None.

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References

[1] Allan SG, Bundred N, Eremin O and Leonard RC. Acute pancreatitis in association with small cell lung carcinoma: potential pitfall in diagnosis and management. Postgrad Med J 1985; 61: 643-644.

[2] Luan J, Kou JY, Huang N, Tao YX, Shi SX, Wu X, Sun YM, Meng DH, Xu JR, Zhou XX, Murtaza G, Bobkov A, Qiao Y, Gao X and Ma N. Inhibition of CHRM3 alleviates necrosis via the MAPK-p38/miR-31-5p/RIP3 axis in L-arginine-induced severe acute pancreatitis. Pancreas 2020; 49: 1335-1341.

[3] Arslan SÇ and Scheidereit C. The prevalence of TNFα-induced necrosis over apoptosis is determined by TAK1-RIP1 interplay. PLoS One 2011; 6: e26069.

[4] Sternby H, Hartman H, Thorlacius H and Regnér S. IL-1β, IL-6, IL-8 and IL-10 are important chronological biomarkers in the inflammatory development of acute pancreatitis. Pancreatology 2018; 18: S100.

[5] Zha L, Gu YX and Zhao M. Clinical efficacy of ulinastatin combined with xuebijing in the treatment of severe acute pancreatitis. Chongqing Med 2018; 47: 1124-1125.

[6] Ronco C. Continuous renal replacement therapy: forty-year anniversary. Int J Artif Organs 2017; 40: 257-264.

[7] Zhang WW. Interpretation of the 2013 Chinese Guidelines for the Diagnosis and Management of Acute Pancreatitis. The 16th Annual National Academic Conference on Emergency Medicine of the Chinese Medical Association Emergency Medicine Branch 2013.

[8] Fan LQ, Jiang SS and Zheng YL. Clinical efficiency of ulinastatin combined with somatostatin in the treatment of patients with severe acute pancreatitis. J Clin Med Pract 2018; 22: 40-42.

[9] Wu JS, Dong LM and Hong WD. Comparison of the prognostic assessment value of APACHE-II criteria, balthazar classification and extra-pancreatic inflammatory scoring system for acute

pancreatitis. 2009 Hong Kong-Beijing-Hangzhou Internal Medicine Forum and 2009 Annual Zhejiang Internal Medicine Conference 2009.

[10] Wang JD and Wang BE. Multi-organ malfunction syndrome (MODS) diagnosis and severity scoring criteria (discussed and approved by the Lushan '95 national critical care emergency medicine symposium). Chin Crit Care Med 1995; 346-347.

[11] Song GD, Zhou J, Song RM, Liu DL, Yu WD, Xie WC, Ma ZL, Gong J, Meng HB, Yang TS and Song ZS. Long noncoding RNA H19 regulates the therapeutic efficacy of mesenchymal stem cells in rats with severe acute pancreatitis by sponging miR-138-5p and miR-141-3p. Stem Cell Res Ther 2020; 11: 420.

[12] Wang GL, Qiu P, Xu LF, Gong M, Wen P and Wen JB. Somatostatin plus ulinastatin and/or gabexate for severe acute pancreatitis. Chin Gen Pract 2018; 21: 4241-4245.

[13] Sheng MH and Zhao JY. Effect of octreotide combined with ulinastatin on oxidative stress and inflammatory factors level in severeacute pancreatitis. Guizhou Med J 2019; 43: 25-27.

[14] Zhao SS, Jin ZC, Yu ZX, Ji MS and Liu J. Clinical observation of early continuous renal replacement therapy combined with ustekin in the treatment of acute severe pancreatitis. J Jiangsu Univ 2016; 26: 88-90.

[15] Wang DM, Zhang Y, Chen L, Xu D, Li X and Chen Y. Effect of somatostatin intensive therapy during blood purification on outcome of patients with severe acute pancreatitis and serum inflammatory factors. Med Pharm J Chin People's Liberation Army 2018; 30: 50-54.

[16] Wu TJ, Zhang LN and Kang CC. The effect of ulinastatin on disbalance of inflammation and immune status in patients with severe sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2013; 25: 219-223.

[17] Sun BR, Zhang C, Lin T, Liu SN, Wang Z, Zhang JY and Liu C. Effect of continuous renal replacement therapy during percutaneous drainage in severe acute pancreatitis patients: a retrospective cohort study. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019; 31: 714-718.

[18] Lou YH. Therapeutic effect of ICU in the treatment of patients with severe acute pancreatitis nd its effect on APACHE II score and biochemical parameters. Med Diet Health 2019; 12: 13-16.

[19] Kang HS, Bai Y, Liu YJ, Wang J, Liu SH, Wang HQ, Ma Z, Ding F and Cui ZB. Linical study of ulinastatin combined with CRRT in the treatment of multiple organ dysfunction syndrome. Chongqing Med 2017; 46: 1478-1481.

[20] Zhang Y. Effect of ulinatatin combined with glutamin treatment on immune function and prognosisin patients with sever acute pancreatitis. Shangdong Univ 2019.

[21] Zhen P, Zhang KP, Zuo ZZ, Zhen ZG and Guo MG. Variation levels of serum inflammatory cytokines in patients with severe acute pancreatitis secondary to pulmonary infection and its clinical value. Chin J Nosocomiol 2020; 30: 1240-1243.