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Original Article

Clinical efficacy of ulinastatin combined with somatostatin for treatment of severe acute pancreatitis and effects on immune function

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Abstract: Objective: The aim of the current study was to investigate clinical efficacy levels of ulinastatin combined with somatostatin for treatment of SAP, examining its effects on immune function. Methods: A total of 106 patients with SAP were selected as subjects. They were divided into the control group (CG) (n = 53) and research group (RG) (n = 53), in accordance with the random number table. The control group was treated with somatostatin, while the research group was treated with somatostatin plus ulinastatin. Treatment efficacy was compared between the two groups. Inflammatory factors, such as serum interleukin-8 (IL-8), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α), were tested. Vascular endothelial function measures, such as nitric oxide (NO), endothelin (ET-1), and von Willebrand factor (vWF), were also measured. Immune function measures, such as levels of CD4+, CD8+, and CD4+/CD8+ were determined. Results: The total effective rate in the research group was 94.34%, higher than the 81.13% in the control group (P<0.05). After treatment, levels of IL-8, CRP, and TNF-α, as well as levels of NO, vWF, ET-1, and CD8+, were lower than those in CG (P<0.05). CD4+ and CD4+/CD8+ levels were higher than those in CG. Recovery times of gastrointestinal function and serum amylase, as well as hospital stays, were shorter than those in CG (P<0.05). Intra-abdominal pressure was lower than that in CG (P<0.05). Recovery times of heart rates, respiration, and body temperatures in the control group were longer than those in RG (P<0.05). There were no significant differences in incidence of adverse reactions between the two groups (P>0.05). Conclusion: Ulinastatin combined with somatostatin can improve clinical efficacy levels of SAP. Relevant mechanisms may be related to the enhancement of patient immune function, reduction of inflammatory response, and improvement of vascular endothelial function.

Keywords: Ulinastatin, somatostatin, severe acute pancreatitis, immune function, vascular endothelial function

Introduction

Severe acute pancreatitis (SAP) is an acute abdominal disease. It is characterized by rapid progression, many complications, and high death rates. Morbidity rates of this disease rank third to fifth for acute abdominal diseases. Some patients die 7 to 10 days after onset [1]. The pathogenesis of SAP is closely related to inflammatory mediators, intestinal barrier dysfunction, and microcirculation disturbance [2]. The inflammation-promoting response and secondary anti-inflammatory response lead to immune function disorders. As a result, the disease is aggravated and the risk of infection increases. Thus, the prognosis of the patients is affected [3]. Therefore, it is of great significance to inhibit inflammatory response and regulate immune function in the treatment of SAP.

Relevant studies have shown that clinical application of inhibiting pancreatic secretion and trypsin inhibitors can improve survival rates [4, 5]. Ulinastatin is a broad-spectrum trypsin inhibitor. It can inhibit the activities of various enzymes, reducing occurrence of SAP complications. A study by Yao Zhenbin, et al. [6] demonstrated that octreotide plus ulinastatin can remarkably improve clinical efficacy in the treatment of SAP, reducing levels of inflammatory cytokines. Somatostatin is an amino acid peptide hormone. It can regulate the release of multiple hormones. Ulinastatin plus somatostatin was used for treatment of SAP patients in the current study. Effects on immune function

Table 1. Comparison of general information

Group	n	Male/Female	Age (years)	Grading		Time of Onset (h)	Basic Disease			
				II	III		Cholecystitis	Gall stones	Hyperlipemia	Others
Control Group	53	28/25	57.53 ± 7.42	41	12	4.55 ± 0.42	14	18	8	13
Research Group	53	26/27	56.97 ± 6.89	43	10	4.50 ± 0.48	17	15	11	10
χ^2/t		0.151	0.403	0.229		0.571	0.699			
P		0.698	0.688	0.632		0.569	1.428			

were observed. Clinical value was also evaluated.

Material and methods

General information

One hundred and six patients with SAP were selected as study subjects. They were treated in the Department of General Surgery, Fuyang District Hospital of Hangzhou, from January 2017 to January 2018. Inclusion criteria: (1) Diagnostic criteria in *Guidelines for Diagnosis and Treatment of Severe Acute Pancreatitis* revised in 2014 by Division of Pancreatic Surgery, Branch of Surgery, Chinese Medical Association were met; (2) Patients aged 18-79 years old; (3) Patients had no disease of the hematologic system or autoimmune system; and (4) Informed consent was obtained. Exclusion criteria: (1) SAP patients with mental diseases; (2) Patients with heart, liver, and kidney dysfunction; (3) SAP patients with malignancies; (4) SAP patients with other acute abdominal diseases; and (5) Patients transferred to the hospital midway, dead with incomplete treatment.

The patients were divided into the control group (CG) (n = 53) and research group (RG) (n = 53). There were no differences in general information between the two groups ($P>0.05$), indicating that the two groups were comparable (**Table 1**).

Methods

All patients with SAP received routine symptomatic treatment after admission, including fasting and water-deprivation, gastrointestinal decompression, antibiotics, and correction of water-electrolytes. CG patients were given somatostatin for injections (Changzhou Siyao Pharmaceuticals Co., Ltd., GYZZ H20043480) at a dose of 6 mg/day. The drug was administrated with a micropump for 24 hours. RG patients were given ulinastatin (Guangdong Techpool Biochemistry Medicine, GYZZ H200-40505) 100-000U + 250 mL 5% glucose solution by intravenous drip, once per day. Efficacy was evaluated after 7 days of continuous treatment.

Outcome measures

(1) Inflammatory factors: A total of 3 mL of venous blood was extracted before and after treatment. The serum was separated by centrifugation. It was then frozen for testing. Serum interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) were determined by enzyme-linked immunosorbent assays (ELISA). Levels of C-reactive protein (CRP) were tested by immunoturbidimetry; (2) Vascular endothelial function: A total of 6 ml of venous blood was collected. The blood was tested after centrifugation. Nitric oxide (NO), endothelin (ET-1), and von Willebrand factor (vWF) were, respectively, measured by nitrate reductase, radioimmunoassay, and immunoturbidimetry; (3) Immune function: CD4+ and CD8+ were, respectively, counted by polychromatic flow cytometry. CD4+/CD8+ was also calculated; (4) Recovery times of gastrointestinal function and blood amylase, as well as hospital stays, were recorded. Intra-abdominal pressure was also measured; (5) Heart rates, respiration, and times of body temperature returning to normal were recorded; (6) Adverse reactions were statistically analyzed.

Efficacy evaluation criteria

Significant improvement: After treatment, SAP related symptoms and signs disappeared. Serum amylase returned to normal. Improvement: After treatment, SAP related symptoms and signs improved. Serum amylase improved but did not return to normal. Ineffectiveness: After treatment, SAP related symptoms and signs were not improved or aggravated. Serum amylase was not signifi-

Table 2. Comparison of efficacy [n (%)]

Group	n	Significant Improvement	Improvement	Ineffectiveness	Total Effective Rate
Research Group	53	36 (67.92)	14 (26.42)	3 (5.66)	50 (94.34)
Control Group	53	27 (50.94)	16 (30.19)	10 (18.87)	43 (81.13)
χ^2					4.296
P					0.038

Table 3. Determination of serum inflammatory factors via enzyme linked immunosorbent assay ($\bar{x} \pm s$)

Group	n	IL-8 (ng/ml)		TNF-α (ng/ml)		CRP (mg/L)	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Research Group	53	95.51 ± 9.72	32.86 ± 4.65	40.49 ± 4.13	22.74 ± 7.53	158.54 ± 37.17	48.36 ± 10.65
Control Group	53	98.04 ± 8.75	53.78 ± 5.31	40.82 ± 4.35	30.66 ± 6.68	161.39 ± 40.23	83.22 ± 12.28
t		1.408	21.578	0.401	5.728	0.379	15.613
P		0.162	<0.001	0.690	<0.001	0.706	<0.001

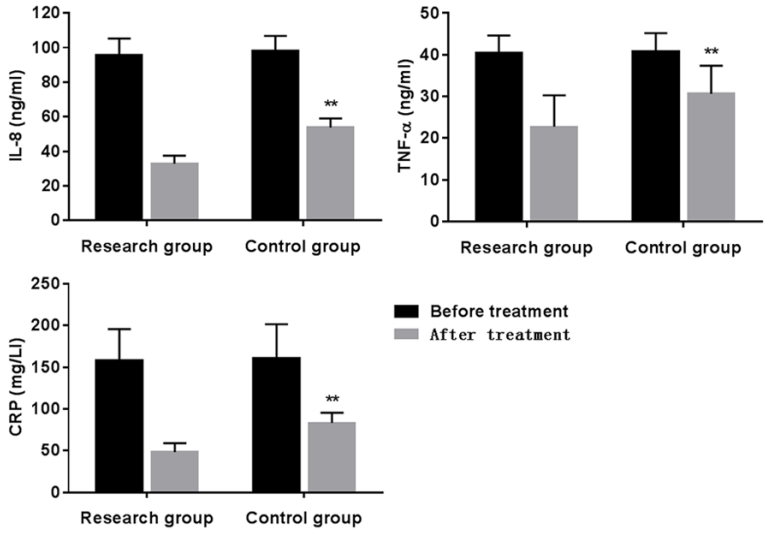

Figure 1. Comparison of IL-8, TNF-α, and CRP levels before and after treatment. Levels of IL-8, TNF-α, and CRP by ELISA in the research group (RG) were lower than those in the control group (CG). Note: **implies *P*<0.01 compared with CG.

cantly reduced. Total effective rate = 1 - ineffective rate.

Statistical analysis

SPSS 19.0 was used to analyze present data. Measurement data are expressed with $\bar{x} \pm s$ and independent sample t-tests were used for comparisons between two groups. Enumeration data are represented with [*n* (%)] and χ^2 tests were applied to compare between the two groups. *P*<0.05 indicates significant differences.

Results

Comparison of efficacy

The total effective rate in RG was higher than that in CG (*P*<0.05). Results suggest that ulinastatin plus somatostatin can better improve the clinical efficacy of SAP (**Table 2**).

Comparison of inflammatory factors

Observing the effects of ulinastatin combined with somatostatin on levels of inflammatory factors, levels of serum IL-8, TNF-α, and CRP were determined by ELISA. Results showed that levels decreased after treatment. Levels in RG were lower than those in CG (*P*<0.05). Results suggest that ulinastatin plus somatostatin can significantly inhibit the inflammatory state in patients with SAP (**Table 3**; **Figure 1**).

Comparison of vascular endothelial function

Investigating the effects on vascular endotherlial function (VEF), levels of VEF related factors were tested. Results show that levels of NO, ET-1, and vWF obviously decreased after treatment. Levels in CG were higher than those in RG (*P*<0.05). This suggests that ulinastatin

Table 4. Comparison of vascular endothelial function ($\bar{x} \pm s$)

Group	n	NO (μmol/L)		ET-1 (pg/ml)		vWF (%)	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Research Group	53	84.22 ± 10.63	54.69 ± 7.15	140.56 ± 6.11	22.74 ± 7.53	260.47 ± 27.64	113.93 ± 10.37
Control Group	53	84.28 ± 11.71	70.37 ± 6.08	142.21 ± 6.34	30.66 ± 6.68	262.59 ± 30.17	192.55 ± 13.21
t		0.028	12.163	1.364	5.728	0.377	34.081
P		0.978	<0.001	0.175	<0.001	0.707	<0.001

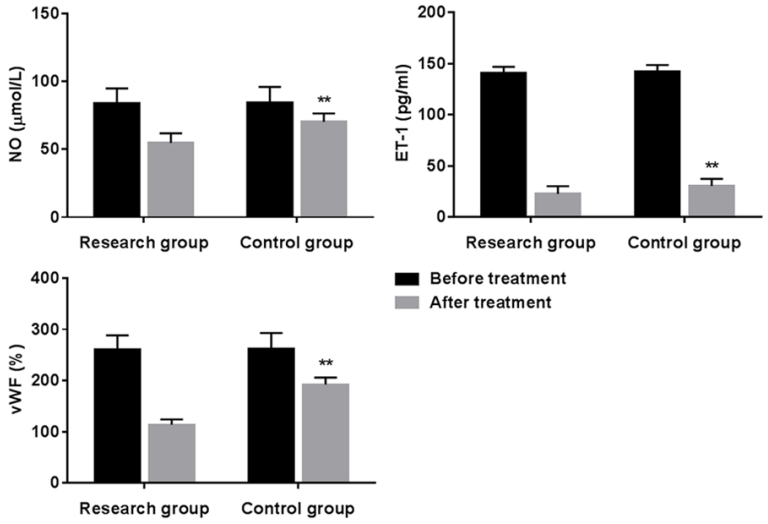

Figure 2. Comparison of NO, ET-1, and vWF levels. Levels of NO by nitric acid reduction method in RG were lower than those in CG after treatment. Levels of ET-1 by radioimmunoassay in CG were higher than those in RG. Levels of vWF by immunoturbidimetry in RG were lower than those in CG. Note: Compared with CG, **revealed *P*<0.01.

plus somatostatin can remarkably improve vascular endothelial function (**Table 4**; **Figure 2**).

Comparison of immune function

Examining the effects on immune function, levels of CD4+ and CD8+ were tested. Results showed that CD4+ and CD4+/CD8+ increased after treatment, while CD8+ decreased. Changes in RG were more remarkable than those in CG (*P*<0.05). Results suggest that immune function in RG can be significantly improved (**Table 5**; **Figure 3**).

Comparison of recovery times of gastrointestinal function and serum amylase, hospital stays, and intra-abdominal pressure

Effects on recovery times of gastrointestinal function and serum amylase, hospital stays, and intra-abdominal pressure were also observed in the current study. Results show that recovery times of gastrointestinal function and serum amylase, as well as hospital stays, in RG were shorter than those in CG. Intra-abdominal pressure was lower than that in CG (*P*< 0.05). Results suggest that ulinastatin combined with somatostatin can shorten recovery times of gastrointestinal function and serum amylase. This is quite beneficial for the recovery of patients (**Table 6**; **Figure 4**).

Comparison of times of respiration, heart rates, and body temperature returning to normal

Effects on respiration, heart rates, body temperatures, and other vital signs were investigated in the current study. Results show that the times of respiration, heart rates, and body temperature returning to normal in RG were shorter than those in CG (*P*<0.05). Results suggest that the vital signs of patients could be remarkably stabilized in RG (**Table 7**; **Figure 5**).

Comparison of adverse reactions

Two cases of transient nausea and 1 case of vomiting occurred in RG. Incidence of total adverse reactions was 5.66% (3/53). One case of transient nausea and 0 cases of vomiting occurred in CG. Total incidence was 1.87% (1/53). There were no remarkable differences in incidence of adverse reactions between the two groups (χ^2 = 1.039, *P* = 0.308).

Discussion

SAP refers to pancreatic acinar damage caused by hyperlipemia, biliary origin, idiopathic, and many other pathogenic factors. Excessive acti-

Table 5. Comparison of immune function ($\bar{x} \pm s$)

Group	n	CD4+ (%)		CD8+ (%)		CD4+/CD8+	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Research Group	53	28.23 ± 4.66	34.17 ± 4.38	32.72 ± 7.93	27.45 ± 5.76	0.86 ± 0.59	1.24 ± 0.76
Control Group	53	28.79 ± 4.34	30.06 ± 4.49	32.28 ± 6.11	30.82 ± 5.27	0.89 ± 0.71	0.93 ± 0.73
t		0.640	4.770	0.320	3.143	0.237	2.142
P		0.523	<0.001	0.750	0.002	0.813	0.035

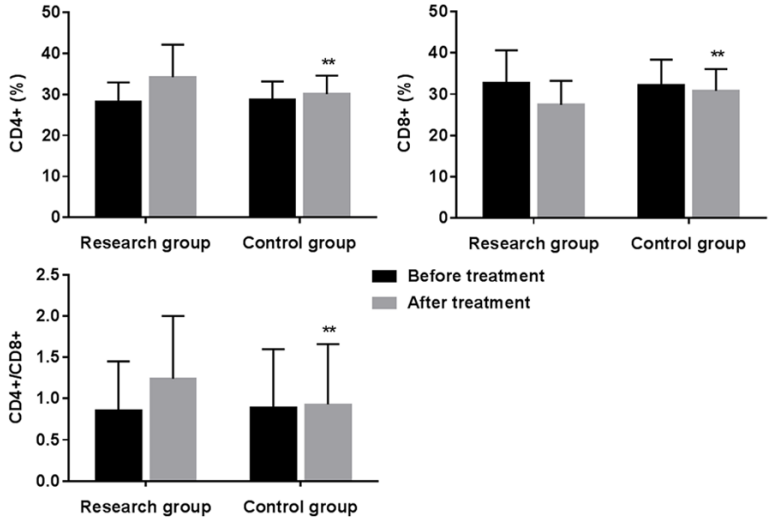

Figure 3. Comparison of CD4+, CD8+, and CD4+/CD8+ levels. Results show that levels of D4+ and CD4+/CD8+ by polychromatic flow cytometry in RG were higher than those in CG. CD8+ levels were lower than those in CG. Note: Compared with CG, **indicates *P*<0.01.

vation and release of trypsin and autodigestion lead to the decomposition of glyceryl phosphatide in pancreatic tissue cells into acid lecithin. As a result, many inflammatory factors are produced. Inflammatory injuries are caused to the pancreas and the surrounding tissues. During the inflammatory response, many toxins are produced and enter the blood circulation. Systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction are caused [7]. Epidemiological characteristics of SAP mainly include pancreatic edema, inflammation, necrosis, and hemorrhaging. Clinical manifestations include epigastric pain, fevers, vomiting, and circulatory disturbance. The case fatality rate of SAP is up to 20%-30% [8]. The massive production of active pancreatin is the key of SAP pathogenesis and progression. Therefore, it is necessary to inhibit the release of pancreatin, alleviate the inflammatory response, and improve prognosis during treatment.

Somatostatin exits in the form of 14-peptide and 328-peptide. It has many biological functions. Somatostatin can regulate endocrine, exocrine, paracrine, and autocrine systems [9]. After treatment with somatostatin, the secretion of pancreatin is reduced. Activation of pancreatin is inhibited. Damage caused by the excessive activation of pancreatin is decreased. Moreover, Oddi's sphincter is relaxed and abdominal pain is relieved. The transcription activity of nuclear factor κB is inhibited. Tissue damage and stress are also alleviated. The release of TNF-α, interleukin, and other inflammatory factors is inhibited. Inflammatory response is relieved. In addition, expression levels of epidermal growth factor in pancreatic cells are upregulated. The proliferation of pancreatic cells is stimulated. The repair of pancreatic cells is promoted [10-12]. Recent studies have found that somatostatin can also improve the immune function of patients with SAP. Ulinastatin is an inflammatory response regulator and hydrolase inhibitor. It is extracted from human urine and produced after being refined. Ulinastatin can inhibit the activities of various proteolytic enzymes, saccharides, and esters hydrolases. The low molecular substances produced by ulinastatin degradation still have inhibitory effects on enzyme activity [13]. Moreover, after treatment with ulinastatin, the release of TNF-α, oxygen radicals, and thromboxane A2 is reduced. Vascular endothelial function is regulated. Moreover, interaction between inflammatory mediators and leukocytes is alleviated. Toxicants entering the blood circulation are reduced. The local microcircula-

Table 6. Comparison of gastrointestinal recovery times, blood amylase recovery times, hospital stays, and intra-abdominal pressure ($\bar{x} \pm s$)

Group	n	Gastrointestinal Recovery Time (d)	Blood Amylase Recovery time (h)	Hospital Stay (d)	Intra-abdominal Pressure (mmHg)
Research Group	53	3.15 ± 0.97	40.19 ± 8.86	12.75 ± 3.64	12.51 ± 1.63
Control Group	53	4.52 ± 1.11	55.84 ± 10.37	17.82 ± 4.46	13.88 ± 1.57
t		6.766	8.353	6.411	4.407
P		<0.001	<0.001	<0.001	<0.001

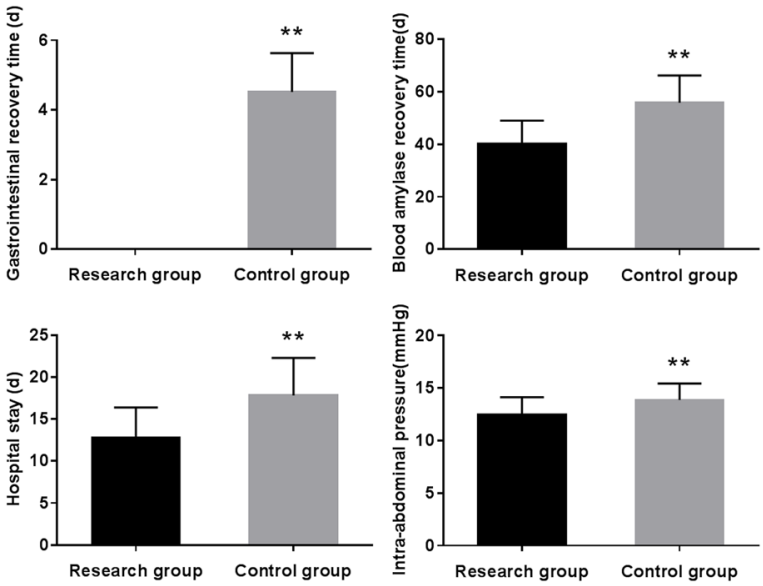

Figure 4. Comparison of gastrointestinal recovery times, blood amylase recovery times, hospital stays, and intra-abdominal pressure. Results show that gastrointestinal recovery times, blood amylase recovery times, hospital stays, and intra-abdominal pressure in RG were superior to those in CG. Patients in RG recovered more rapidly. Note: **means $P<0.01$ compared with CG.

tion is improved. Further damage to the pancreas is prevented. Somatostatin plus ulinastatin has synergistic effects, enhancing the inhibitory effects on inflammatory response. In addition, the development of SAP into SIRS, as well as multiple organ dysfunction, is prevented.

Current study results showed that recovery times of respiration, heart rates, body temperatures, and blood amylase in CG were longer than those in RG. Hospital stays were significantly shortened in RG. Improvements in intra-abdominal pressure were superior to those in CG. Results suggest that ulinastatin combined with somatostatin can effectively improve the clinical symptoms of SAP, promoting the recovery of patients. Present conclusions are consistent with those of previous studies [14].

Local and systemic inflammatory responses are the malignant results of SAP progression. Inflammatory mediators and factors play a bridging role in the pathological process. IL-8 is an inflammatory medium, also known as neutrophil factor. IL-8 has chemotactic effects on immune cells. It plays an important role in inflammatory response and immune response [15]. TNF-α is a peptide hormone. It is mainly produced by monocytes/macrophages. TNF-α is involved in the processes of inflammatory response and immune response [16]. CRP is an acute phase reactive protein. It can reflect the degree of inflammatory response. Therefore, it is an important measurement tool for diagnosis of inflammation clinically [17]. For patients with SAP, the body is in a state of high inflammatory response. A large quantity of IL-8, TNF-α, and CRP are produced and released. Expression levels are abnormally increased [18]. Current results showed that levels of IL-8, TNF-α, and CRP were reduced after treatment. Changes in RG were more significant. Results suggest that ulinastatin combined with somatostatin can alleviate inflammatory response.

Pancreatic microcirculation disorder is an important factor in the occurrence and development of SAP. It has been considered the main cause of pancreatic ischemic necrosis, hemorrhaging, and autolysis [19]. Due to the reduction of local blood flow in SAP, pancreatic tissue necrosis, pancreatic vasoconstriction, thrombosis, and vascular endothelial injury are often caused. After vascular endothelial inju-

Table 7. Comparison of times of respiratory and heart rate returning to normal ($\bar{x} \pm s$)

Group	n	Respiratory Recovery Time (h)	Heart Rate Returns to Normal Time (h)	Body Temperature Returns to Normal Time (d)
Research Group	53	96.37 ± 10.24	93.05 ± 11.70	2.43 ± 0.98
Control Group	53	122.85 ± 12.97	65.63 ± 8.29	3.71 ± 1.02
t		11.666	13.921	6.588
P		<0.001	<0.001	<0.001

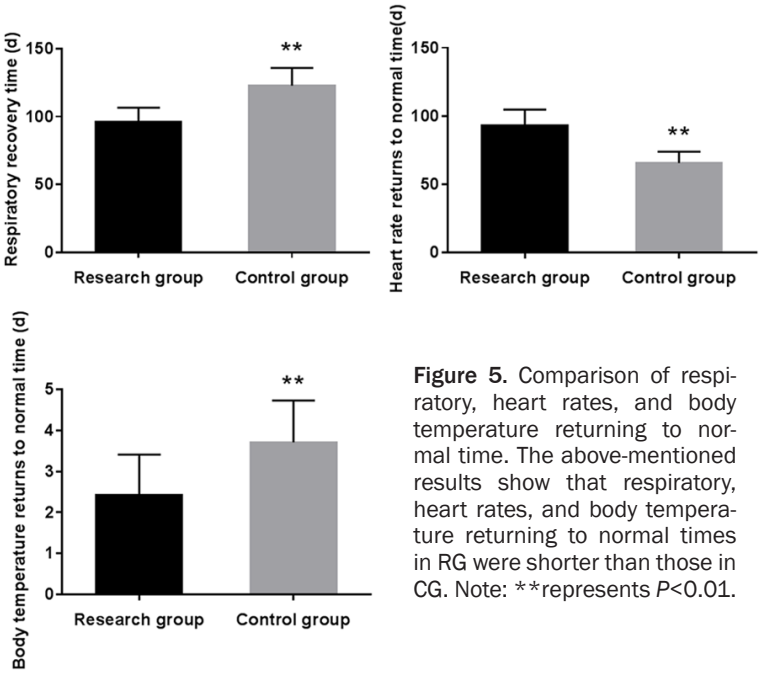

Figure 5. Comparison of respiratory, heart rates, and body temperature returning to normal time. The above-mentioned results show that respiratory, heart rates, and body temperature returning to normal times in RG were shorter than those in CG. Note: **represents *P*<0.01.

ries occur, the body is stimulated to release NO, ET-1, vWF, and other substances. Increased NO, ET-1, and vWF stimulate the platelet to aggregate in the vascular wall. As a result, the blood vessels are narrower. Pancreatic ischemia is aggravated. Thus, further development of SAP is promoted [20]. The current study showed that levels of NO, ET-1, and vWF decreased after treatment. Changes in RG were more remarkable. Results suggest that ulinastatin plus somatostatin can significantly improve vascular endothelial function, in accord with previous studies [21].

Levels of CD4+, CD8+, and CD4+/CD8+ reflect the distribution of T-cell subsets and immune function [22]. CD^+_4 can migrate, activate, and proliferate under the action of inflammatory mediators. Next, they are transformed into granulocyte-macrophage colony stimulating factors. Thus, the number of CD^+_4 is increased [23]. CD^+_4 directly participates in the activation of T-cells. It plays an immunomodulatory role through the synthesis and release of TNF-α, IL-2, and other cytokines. Moreover, the pathogens *in vivo* are eliminated [24]. CD8+ is a cytotoxic T-cell subset. It can eradicate toxins or parasite infected cells and tumor cells [25]. One study demonstrated that levels of CD4+ and CD4+/CD8+ in peripheral blood of patients with SAP were lower than those in healthy people. Levels of CD8+ were remarkably increased [25]. Current study results showed that increases of CD4+ and CD4+/CD8+ and decreases of CD8+ in RG were more obvious than those in CG. Results suggest that ulinastatin plus somatostatin can enhance immune function. However, the sample size in the current study was small. Therefore, present conclusions should be validated by further expanding the sample size via future multicenter studies.

In summary, ulinastatin combined with somatostatin can enhance the clinical efficacy of SAP. Relevant mechanisms may be related to several significant roles. This combination enhances immune function, alleviates inflammatory response, and improves vascular endothelial function. Thus, patient rehabilitation is accelerated. Therefore, it is worthy of promotion.

Disclosure of conflict of interest

None.

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