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Original Article

Ulinastatin combined with somatostatin enhances disease control and modulates serum inflammatory factors in patients with severe pancreatitis

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Abstract: Objective: This study was designed to explore the effects of ulinastatin combined with somatostatin on disease control and serum inflammatory factors in patients with severe pancreatitis. Methods: The data of 80 patients with severe pancreatitis treated in the First Affiliated Hospital of Jiangxi Medical College from May 2020 to April 2022 were analyzed retrospectively. Among them, 36 patients treated with somatostatin alone (3 mg somatostatin added in 50 mL normal saline) on the basis of standard treatment were assigned to a control group, and the other 44 patients treated with both ulinastatin (100,000 U of ulinastatin injection added in 250 mL 5% glucose solution) and somatostatin (3 mg somatostatin added in 50 mL normal saline) were enrolled into a study group. The levels of serum inflammatory factors (interleukin-1β (IL-1β), interleukin-6 (IL-6), and soluble intercellular adhesion molecule-1 (sICAM-1)), biochemical indexes (C-reactive protein, white blood cell count, and serum amylase) and gastrointestinal function indexes (motilin and gastrin) in the two groups were analyzed and compared before and after treatment. Additionally, the alleviation of clinical symptoms, treatment response and occurrence of adverse reactions were compared between the two groups. The mortality rate of patients within 1 month after the treatment was evaluated, and the risk factors affecting the prognosis were analyzed through logistics regression. Results: Before treatment, there was no significant difference between the two groups in the levels of IL-1β, IL-6 and sICAM-1 ($P>0.05$), while after treatment, the levels of all three factors decreased significantly in both groups ($P<0.0001$), with more notable decreases in the study group than those in the control group ($P<0.0001$). Before treatment, the two groups were not significantly different in the levels of C-reactive protein, white blood cell count, and serum amylase ($P>0.05$), while after treatment, all the three levels decreased notably in both groups ($P<0.0001$), with notably lower levels in the study group than those in the control group ($P<0.0001$). Before treatment, the levels of motilin and gastrin in the two groups were not significantly different ($P>0.05$), while after treatment, motilin increased significantly and gastrin decreased significantly in both groups ($P<0.0001$), and the study group showed a notably higher motilin level and a notably lower gastrin level than the control group ($P<0.0001$). The study group experienced a significantly earlier disappearance time of abdominal distension and abdominal pain and a significantly shorter hospitalization time than the control group ($P<0.0001$). Moreover, the study group showed a notably higher overall response rate than the control group ($P=0.029$), and presented a notably lower incidence of adverse reactions than the control group ($P=0.036$). According to univariate analysis, age, onset time, Acute Physiology and Chronic Health Evaluation II score and therapeutic regimen were the factors impacting the patients' prognosis. According to logistics regression analysis, therapeutic regimen was an independent risk factor affecting the prognosis. Conclusion: Compared with somatostatin alone, ulinastatin combined with somatostatin is more effective in the treatment of severe pancreatitis. The combination can substantially alleviate the inflammatory response and improve the gastrointestinal function and clinical symptoms of patients, without increasing adverse reactions. Therefore, ulinastatin combined with somatostatin is worthy of clinical promotion.

Keywords: Ulinastatin, somatostatin, severe pancreatitis, clinical symptoms, serum inflammatory factors

Introduction

Pancreatitis is a disease triggered by the self-digestion of trypsin [1], and its development is mostly related to diet. Excessive eating can bring overload to the pancreas and hinder the excretion of pancreatic juice, thus triggering pancreatitis [1, 2]. With the change of lifestyle, increase of pressure, improper diet, and development of bile duct diseases, pancreatitis has shown a gradually increasing incidence [3]. Severe pancreatitis is a special type of acute pancreatitis with systemic and local complications, as well as a dangerous acute abdomen with various complications and a high mortality (15-30%) [4]. It is an inflammatory disease involving autodigestion of the pancreas, with an annual incidence of 20-80 per 100,000 individuals [5]. Patients with pancreatitis often suffer severe upper abdomen pain that radiates to the back, as well as nausea, vomiting, abdominal distension, systemic inflammatory reactions etc. In severe cases, the patients can have life-threatening respiratory failure and acute renal failure [6]. Accordingly, the therapy for pancreatitis has always been a focus in clinical research.

The main treatment methods for severe pancreatitis include non-surgical treatment (conservative treatment) and surgical treatment, with a trend from surgical treatment to conservative treatment [7, 8]. At the current stage, the primary approaches are anti-infection and food and water fasting combined with somatostatin, but the long treatment cycle compromises the overall response of patients [9, 10]. Accordingly, it is necessary to combine the conventional treatment with other drugs to shorten the treatment cycle and timely alleviate the symptoms. As a synthetic bioactive substance of 14 peptides, synthetic somatostatin is exactly the same as natural somatostatin in chemical structure and mechanism of action, which can inhibit the secretion of pancreatic enzyme, lower the pressure of pancreatic duct, relax the sphincter of Oddi, and reduce the pancreatic juice in the pancreatic duct to enter the pancreatic tissue, thus decreasing the pancreatic self-digestion [11-13]. Somatostatin is believed to have a protective effect on pancreatic cells and an ability to prevent the progress of pancreatitis, so it is usually adopted for severe pancreatitis in clinical practice. He et al. [14] revealed that ulinastatin improved the clinical prognosis of patients with severe acute pancreatitis, but its efficacy varied with dosage. Ulinastatin is a protease inhibitor that can inhibit inflammation and reduce the activity of various proteases, so it is of great significance in preventing multiple organ failure [15, 16]. There are studies about ulinastatin or somatostatin on severe pancreatitis, but the combination of the two in this disease is rarely studied.

Accordingly, with the purpose of providing reference for the future therapy of severe pancreatitis, this study explored the clinical effect of ulinastatin combined with somatostatin on disease control and serum inflammatory factors in patients with severe pancreatitis and analyzed the factors impacting the patient prognosis.

Materials and methods

Sample information

The data of 110 patients with severe pancreatitis treated in the First Affiliated Hospital of Jiangxi Medical College from May 2020 to April 2022 were analyzed retrospectively.

Ethical statement

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Jiangxi Medical College.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients who met the diagnostic criteria of severe pancreatitis [17]. To be specific, patients had sudden dysfunction in one or more organs, accompanied by severe metabolic dysfunction, tissue necrosis, infection, etc.; patients showed obvious muscle, abdominal distension, intestinal sound weakening or disappearance, etc. according to abdominal examination; patients showed pancreatic tissue necrosis according to enhanced CT; (2) patients with Acute Physiology and Chronic Health Evaluation II (APACHEII) score above 8 points [18]; (3) patients who received treatment within 48 h from onset; (4) patients without a history of pancreatitis; (5) patients who had not received abdominal surgery within 6 months; (6) patients with detailed clinical case data.

Exclusion criteria: (1) patients with serious organic lesions; (2) patients with coagulation

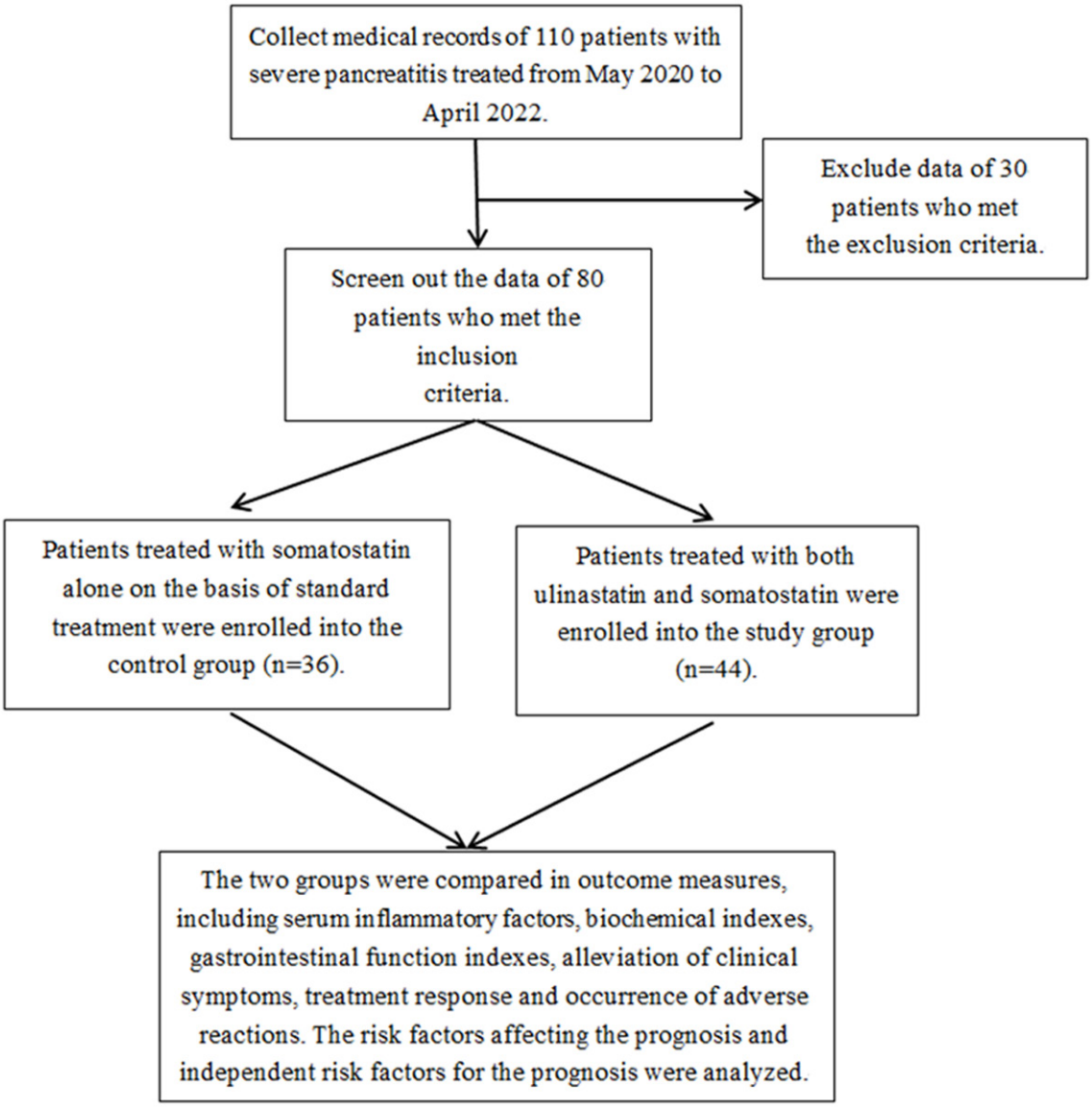

Figure 1. Flow chart of the study.

dysfunction; (3) patients with an allergic constitution or contraindications for drugs adopted in this study; (4) patients during pregnancy or lactation; (5) patients with infectious diseases; (6) patients with heart, liver or kidney dysfunction.

Sample selection

According to the criteria, 80 patients who met the enrolment requirements were selected from a total of 110 patients. Among them, 36 patients treated with somatostatin alone on the basis of standard treatment were assigned to a control group, and the other 44 patients treated with both ulinastatin and somatostatin were assigned to a study group. The flow chart of the study is shown in **Figure 1**.

Therapeutic regimens

Patients in the control group received routine standard treatment. Specifically, each patient was given anti-infection, spasmolysis, fluid replacement, acid suppression, maintenance of water and electrolyte balance, fasting, gastrointestinal decompression and nutritional support [19]. The vital signs of the patient were carefully monitored to address potential abnor-

mity in time [19]. Additionally, the patient was given 3 mg somatostatin injection (Beijing SL Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H20054016; specification: 3 mg/piece) mixed in 50 mL normal saline through intravenous infusion at a speed of 4 mL/h for 10 days. Patients in the study group were treated with additional ulinastatin injection based on treatment in the control group. Each patient was given 100,000 U of ulinastatin injection (Guangdong Techpool Bio-Pharma Co., Ltd., SFDA approval number: H20040506; specification: 100,000 U) mixed in 250 mL 5% glucose solution through intravenous infusion, 3 times/day, for 10 days.

Outcome measures

Primary outcome measures: (1) Serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1): Before and after 10 days of treatment, 5 mL fasting elbow venous blood was collected from each patient in the morning, followed by 10-min centrifugation (3000 r/min) to separate serum. The serum was stored at -80°C for examination. Then the levels of IL-1β, IL-6 and sICAM-1 in the serum were determined through enzyme-linked immunosorbent assay. (2) Biochemical indexes: The biochemical indexes (C-reactive protein, white blood cell count and blood amylase) of the two groups were detected and compared. (3) Response rate: The efficacy in the two groups was evaluated and compared according to the following criteria: Cured: The clinical symptoms and signs disappeared within 10 days after the treatment; the CT results revealed a normal pancreas, and serum amylase level returned to normal. Markedly effective: The clinical symptoms and signs were obviously alleviated within 10 days, and the pancreas and serum amylase were both basically normal. Effective: The clinical symptoms and signs were obviously alleviated within 10 days, and the pancreas was close to normal, with serum amylase level decreased by over 50%. Ineffective: None of the above criteria was met [20]. Total response rate = (number of cured cases + that of cases with markedly effective response + that of cases with effective response)/the total number of patients ×100%.

Secondary outcome measures: (1) The gastrointestinal function indexes, including motilin and gastrin, were determined and compared between the two groups. (2) The disappearance time of abdominal distension and abdominal pain, as well as hospitalization time were recorded and compared between the two groups. (3) The incidence of adverse reactions including nausea and vomiting, bowel sound, abdominal pain, and rash was recorded and compared between the two groups. (4) The mortality rate of the patients within 1 month was evaluated. Then the risk factors affecting the prognosis were analyzed through logistics regression, and multivariate analysis was conducted to analyze independent risk factors for poor prognosis through the backward LR method.

Statistical analyses

This study adopted SPSS22 statistical software for statistical analyses of acquired data, and GraphPad Prism 8 for visualization of data. Counting data were expressed by percentage, and compared between groups using the chi-square test. Measurement data were described by mean ± standard deviation (SD). Their intra-group before-after comparison was conducted using the paired sample t test, and the between-group comparison was conducted using the independent sample t test. The disappearance time of abdominal distension and abdominal pain were compared using the log rank test and analyzed using K-M plotting. $P<0.05$ indicates a statistically significant difference.

Results

Baseline data of patients

There were no significant differences between the control and study groups in age, gender, body mass index (BMI), onset time, and Acute Physiology and Chronic Health Evaluation II (APACHEII) scores ($P>0.05$, **Table 1**), so the two groups were comparable.

Comparison of serum inflammatory factors between the two groups

Before treatment, the two groups were not significantly different in the levels of IL-1β, IL-6 and sICAM-1 ($P>0.05$), while after treatment, the levels of the three factors decreased sig-

Table 1. Comparison of baseline data between the two groups

Factors	Study group (n=44)	Control group (n=36)	X^2 value	*P* value
Age			0.0147	0.904
≥55 years	14	11		
<55 years	30	25		
Gender			0.115	0.734
Male	20	15		
Female	24	21		
BMI			3.285	0.070
≥23 kg/m^2	35	22		
<23 kg/m^2	9	14		
Onset time			0.005	0.945
≥20 h	18	15		
<20 h	26	21		
APACHEII score				
≥11 points	19	17	0.131	0.718
<11 points	25	19		

BMI: body mass index; APACHEII score: Acute Physiology and Chronic Health Evaluation score.

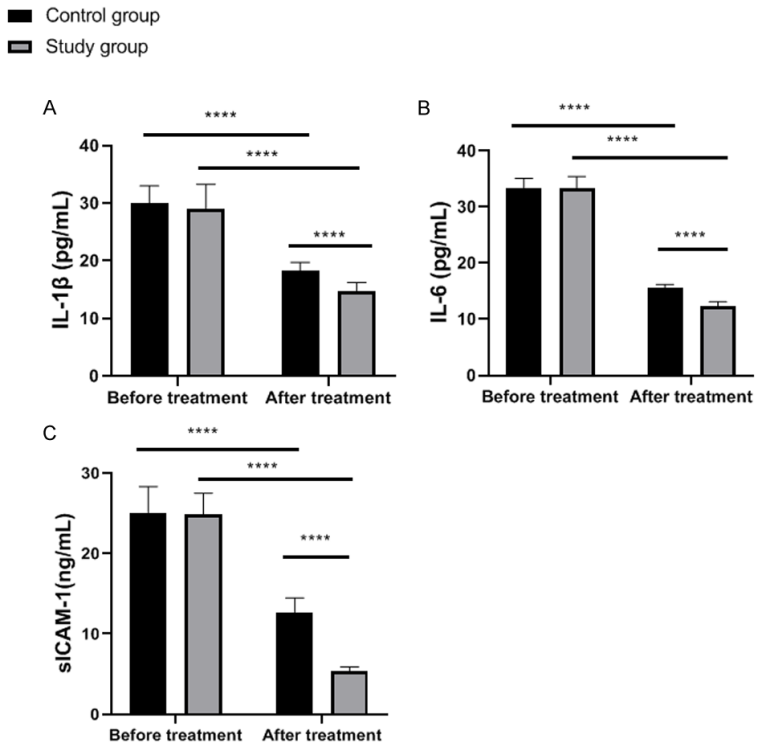

Figure 2. Comparison of serum inflammatory factors between the two groups. A: Comparison of IL-1β between the two groups before and after treatment; B: Comparison of IL-6 between the two groups before and after treatment; C: Comparison of sICAM-1 between the two groups before and after treatment. Note: ****P<0.0001; IL-1β: interleukin-1β; IL-6: interleukin-6; sICAM-1: soluble intercellular adhesion molecule-1.

nificantly in both groups (P<0.0001), and the decreases were more significant in the study group than those in the control group (P<0.0001, **Figure 2**).

Comparison of biochemical indexes between the two groups

Before treatment, there was no significant difference between the two groups in the levels of C-reactive protein, white blood cell count, and serum amylase (P<0.05), while after treatment, all three levels decreased significantly in both groups (P<0.0001), with significantly lower levels in the study group than those in the control group (P<0.0001, **Figure 3**).

Comparison of gastrointestinal function indexes between the two groups

Before treatment, the levels of motilin and gastrin in the two groups were not significantly different (P>0.05), while after treatment, motilin increased notably and gastrin decreased notably in both groups (P<0.0001). Further analysis found that after treatment, the study group showed a significantly higher motilin level and a significantly lower gastrin level than the control group (P<0.0001, **Figure 4**).

Comparison of disappearance time of abdominal distension and abdominal pain, as well as hospitalization time between the two groups

The study group experienced a significantly earlier disappearance of abdominal distension and abdominal pain and a significantly shorter

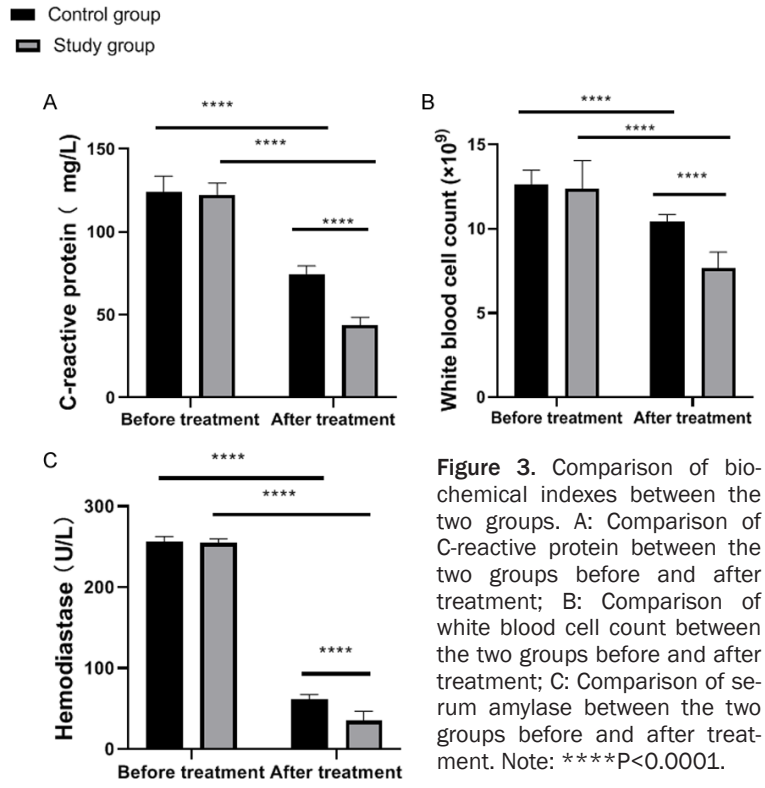

Figure 3. Comparison of biochemical indexes between the two groups. A: Comparison of C-reactive protein between the two groups before and after treatment; B: Comparison of white blood cell count between the two groups before and after treatment; C: Comparison of serum amylase between the two groups before and after treatment. Note: ****P<0.0001.

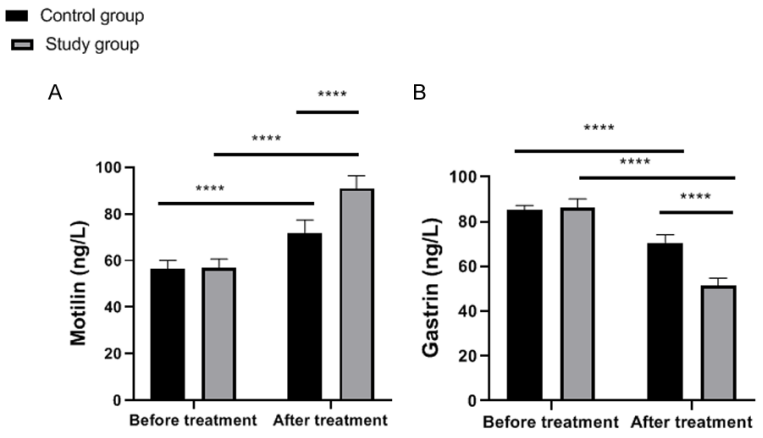

Figure 4. Comparison of gastrointestinal function indexes between the two groups. A: Comparison of motilin level between the two groups before and after treatment; B: Comparison of gastrin level between the two groups before and after treatment. Note: ****P<0.0001.

hospitalization time than the control group (P<0.0001, **Figure 5**).

Comparison of efficacy between the two groups

The study group showed a significantly higher overall response rate than the control group (P=0.029, **Table 2**).

Incidence of adverse reactions in the two groups

The study group showed a significantly lower incidence of adverse reactions than the control group (P=0.036, **Table 3**).

Analysis of factors affecting the prognosis

The study group showed a mortality rate of 6.82%, with 3 deaths and 41 survivors, while the control group showed a mortality rate of 22.22%, with 8 deaths and 28 survivors. The two groups were significantly different in the 1-month mortality rate (P=0.0465). According to the survival, patients who died were included in a poor-prognosis group (n=11), and the survived ones were included in a good-prognosis group (n=69). Univariate analysis was conducted to analyze the clinical data of the two groups. As a result, age, onset time, APACHEII score and therapeutic regimen were found to be factors impacting the patient prognosis (**Table 4**). The above indicators with significant differences were assigned (**Table 5**) and subjected to multivariate analysis. According to logistics regression analysis, therapeutic regimen was found to be an independent risk factor affecting the prognosis (**Table 6**).

Discussion

Severe pancreatitis is characterized with pancreatic organ necrosis or dysfunction, which can induce intense inflammatory reaction in local pancreas tissue. This disease progresses rapidly and is highly life-threatening, with a high mortality [21, 22]. Currently, the main treatment methods for severe pancreatitis involve inflammation control and functional support,

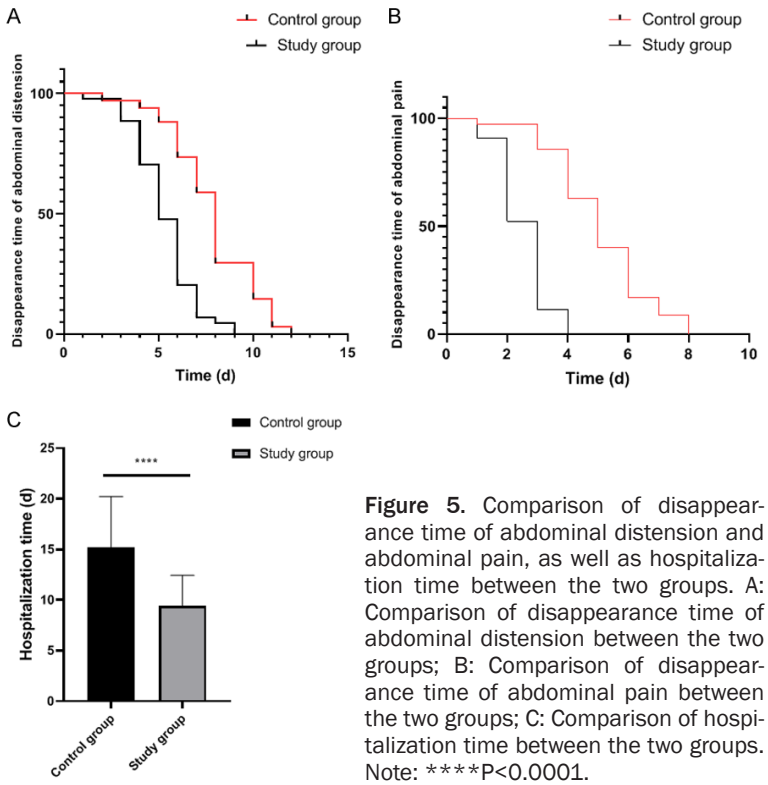

Figure 5. Comparison of disappearance time of abdominal distension and abdominal pain, as well as hospitalization time between the two groups. A: Comparison of disappearance time of abdominal distension between the two groups; B: Comparison of disappearance time of abdominal pain between the two groups; C: Comparison of hospitalization time between the two groups. Note: ****P<0.0001.

but there are still limitations in relieving symptoms in time and shortening the hospital stay [23]. Ulinastatin is a single-chain polypeptide glycoprotein that can suppress various trypsin and pancreatin, so it is commonly adopted to treat pancreatitis [24]. Somatostatin, a polypeptide hormone drug, is also often adopted in the treatment of pancreatitis, and its main mechanism is to suppress the secretion of pancreatin [25]. Therefore, this study explored the clinical efficacy of the combination of somatostatin and ulinastatin in severe pancreatitis to provide a theoretical basis for future treatment of severe pancreatitis.

Inflammatory factors play an important role in regulating and mediating the process of inflammation [26]. IL-1β, IL-6, and sICAM-1 are all important inflammatory cytokines that reflect systemic inflammation [27]. Accordingly, this study examined the levels of the three factors in the two groups before and after treatment and found no significant difference between the two groups before treatment, but significantly decreased levels were identified in the three factors in the two groups after treatment, and the decreases were more significant in the study group than those in the control group. These results imply that ulinastatin combined with somatostatin could strongly lower the levels of inflammatory factors and alleviate inflammatory response in patients with severe pancreatitis. Yang et al. [20] pointed out that ulinastatin combined with somatostatin could lower the levels of IL-10, IL-18 and TNF-α in patients with severe acute pancreatitis, which is consistent with the results of the present study. Moreover, this study compared the biochemical indexes in the two groups before and after treatment. According to the results, the two groups were not significantly different in the levels of C-reactive protein, white blood cell count, and serum amylase before treatment, while after treatment, those levels decreased notably in both groups, with significantly lower levels in the study group than those in the control group. It is indicated that the combined regimen is more conducive to improving the biochemical indexes of patients and alleviating the inflammatory reaction.

Severe pancreatitis may involve the intestine and stomach, triggering flatulence and intestinal paralysis symptoms, as well as stomach symptoms [28]. In order to understand the positive effect of ulinastatin combined with somatostatin on gastrointestinal function and clinical symptoms of patients with severe pancreatitis, this study analyzed the gastrointestinal function indexes in the two groups before and after treatment. According to the results, before treatment, the levels of motilin and gastrin in the two groups were similar, while after treatment, both groups showed notably increased motilin and decreased gastrin, with a significantly higher motilin and a lower gastrin in the study group than those in the control group. The results imply that the combination treatment is beneficial to improving the gastrointestinal function of patients. Moreover, the study group experienced a notably earlier disappearance of abdominal distension and

Table 2. Efficacy in the two groups [n (%)]

Group	Cured	Markedly effective	Effective	Ineffective	Response (%)
Study group (n=44)	16 (36.36)	15 (34.09)	10 (22.72)	4 (6.81)	40 (93.18)
Control group (n=36)	7 (19.44)	9 (25.00)	10 (27.78)	10 (27.78)	26 (72.22)
X^2			0.269		4.789
P value			0.604		0.029

Table 3. Incidence of adverse reactions in the two groups [n (%)]

Group	Nausea and vomiting	Bowel sound	Abdominal pain	Rash	Adverse reactions
Study group (n=44)	1 (2.27)	1 (2.27)	0 (0.00)	0 (0.00)	2 (4.54)
Control group (n=36)	3 (8.33)	2 (5.56)	1 (2.78)	1 (2.78)	7 (19.45)
X^2	1.531	0.591	1.238	1.238	4.402
P value	0.216	0.442	0.266	0.266	0.036

Table 4. Univariate analysis

Factors	Good prognosis group (n=69)	Poor prognosis group (n=11)	X^2 value	*P* value
Age			6.226	0.013
≥55 years	18	7		
<55 years	51	4		
Gender			0.015	0.902
Male	30	5		
Female	39	6		
BMI			1.737	0.188
≥23 kg/m^2	51	6		
<23 kg/m^2	18	5		
Onset time			8.661	0.003
≥20 h	24	9		
<20 h	45	2		
APACHEII score			6.985	0.008
≥11 points	27	9		
<11 points	42	2		
Therapeutic regimen			3.962	0.047
Somatostatin	28	8		
Ulinastatin + somatostatin	41	3		

BMI: body mass index; APACHEII score: Acute Physiology and Chronic Health Evaluation score.

Table 5. Assignment

Factors	Assignment
Age	<55 years =0, ≥55 years =1
Onset time	<20 h =0, ≥20 h =1
APACHEII score	<11 points =0, ≥11 points =1
Therapeutic regimen	Ulinastatin + somatostatin =0, Somatostatin =1
Prognosis	Good prognosis =0, Poor prognosis =1

APACHEII score: Acute Physiology and Chronic Health Evaluation score.

abdominal pain, as well as a significantly shorter hospitalization time than the control group. These results indicate that the combined regimen can alleviate the clinical symptoms of patients with severe pancreatitis more quickly and effectively. The reasons may be as follows: (1) Somatostatin is widely distributed in human gastrointestinal tract and other tissues, and treatment with somatostatin can effectively inhibit the secretion of trypsin and reduce the amount of trypsin released into the blood [29].

Table 6. Multivariate logistic regression analysis

Factors	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B)	
							Lower limit	Upper limit
Age	-1.004	0.712	1.988	1	0.159	0.366	0.091	1.480
Onset time	0.610	0.759	0.646	1	0.421	1.841	0.416	8.150
APACHEII score	-0.548	0.719	0.581	1	0.446	0.578	0.141	2.367
Therapeutic regimen	-2.332	1.076	4.695	1	0.030	0.097	0.012	0.801

APACHEII score: Acute Physiology and Chronic Health Evaluation score.

(2) Somatostatin can stimulate the reticuloendothelial system, improve serum levels, effectively inhibit the secretion of inflammatory factors, and thus weaken the inflammatory reaction [30]. (3) Somatostatin plays a role in protecting gastric mucosa. It can be concluded that the main role of somatostatin in the treatment of pancreatitis is to inhibit pancreatic secretion, reduce the production of inflammatory factors, and effectively control the development of pancreatitis [31]. Treatment of somatostatin can alleviate most of the clinical manifestations, such as abdominal pain and abdominal distension, so that the patients gradually return to health. (4) Ulinastatin is a broad-spectrum trypsin inhibitor, which can effectively inhibit trypsin, elastase, chymotrypsin and hyaluronidase, thus strongly suppressing inflammatory factors, reducing inflammatory reaction, and alleviating organ injury [32-34]. The combined action of the two drugs can effectively alleviate the clinical symptoms of patients and improve their physical condition. Wang et al. [35] revealed that somatostatin was an effective drug for acute pancreatitis, but the combination of ulinastatin and salvia miltiorrhiza delivered greatly higher efficacy, which can support the results of this study. This study also analyzed the treatment efficacy and adverse reactions of the two groups, and found a notably higher overall response rate and a significantly lower incidence of adverse reactions in the study group than those in the control group. These data imply that combined treatment is better and safer. At the end of the study, we analyzed the factors affecting the prognosis of patients, and found that therapeutic regimen was an independent risk factor influencing the prognosis.

This study has verified the control effect of ulinastatin plus somatostatin on severe pancreatitis and their influence on serum inflammatory factors, but the study still has some limitations. First of all, the limited sample size in this study may result in some deviation in the conclusion of the study. In addition, the long-term prognosis of patients was not followed up, so the effect of ulinastatin combined with somatostatin on the long-term prognosis of patients with severe pancreatitis still requires further investigation. Moreover, the mechanism of ulinastatin combined with somatostatin in treating severe pancreatitis needs confirmation by basic experiments in vitro. Therefore, we hope to conduct further comprehensive analyses on the application of ulinastatin combined with somatostatin in severe pancreatitis in the future to acquire more experimental results.

To sum up, compared with somatostatin alone, ulinastatin combined with somatostatin is more effective in the treatment of severe pancreatitis. The combination can substantially alleviate the inflammatory response, as well as improve the gastrointestinal function and clinical symptoms of patients, without increasing adverse reactions. Accordingly, ulinastatin combined with somatostatin is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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