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Original Article

Ulinastatin combined with somatostatin improves intestinal function recovery and treatment efficiency in severe acute pancreatitis

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Abstract: Objective: To explore the clinical efficacy of ulinastatin combined with somatostatin in treatment of severe acute pancreatitis (SAP) and its effects on immune function. Methods: From Sep 2016 to Jul 2018, 82 patients with SAP admitted to Weihai Central Hospital were selected and were randomly divided into an observation group and a control group. The control group was treated with routine therapy and the observation group was also treated with ulinastatin combined with somatostatin in addition to the treatment adopted for the control group. The two groups were compared in movement of laboratory indexes, intestinal function recovery, occurrence of complications and effective rate of treatment, and their levels of CD4+, CD8+, CD4+/CD8+, IgA, IgM and IgG levels in whole blood were detected. Results: After treatment, both the observation group and the control group showed significantly decreased laboratory indexes including white blood cell (WBC), C-reactive protein (CRP), amylase (AMS), total bilirubin (TBIL) and alanine aminotransferase (ALT) (all $P<0.05$), and the observation group showed a more significant decrease than the control group ($P<0.05$); the observation group experienced significantly shorter duration for disappearance of abdominal pain, temperature recovery time and time of abdominal distention, nausea and vomiting and upper abdominal pain recovering to normal, than the control group (all $P<0.05$), and the control group showed significantly higher complication rates, significantly lower effective rate of treatment and significantly higher CD4+, CD8+ and CD4+/CD8+ levels than the observation group (all $P<0.05$). After treatment, the control group still showed no significant difference with the observation group in IgA and IgM levels (both $P<0.05$), but showed significantly lower IgG level than the observation group ($P>0.05$). Conclusion: With high drug safety, ulinastatin combined with somatostatin is effective for SAP patients, because it can improve intestinal function recovery, treatment efficiency, body immunity, lower complication rates and speed up rehabilitation process.

Keywords: Ulinastatin, somatostatin, severe acute pancreatitis, clinical efficacy, immune function

Introduction

Severe acute pancreatitis (SAP), a common acute abdominal issue in the department of gastroenterology, usually shows as acute digestive pancreatic inflammation and para-pancreatic tissue inflammation for surgical trauma, biliary tract diseases, poor dietary habits and infection, whose main clinical features include morphological changes of the pancreatitis, hemorrhagic necrosis, fever and even shock [1-3]. Unstable and continuously deteriorated SAP may cause multiple organ failure, compensation disorder in hepatic and renal function and other risks, and SAP usually occurs and develops acutely with high mortality [4, 5]. Therefore, it is a necessary task to take effective measures to control the inflammatory response and slow down malignant lesions to save patients.

In addition to routine treatment such as proton pump inhibitors and antibiotics, ulinastatin and somatostatin inhibitors are also often adopted in a combined way to treat SAP clinically [6-8]. A study has revealed that SAP is related to pancreatin activation, inflammatory factor level elevation and pancreatic microcirculation damage [9]. Somatostatin can suppress contraction and digestive enzyme secretion rates of the gallbladder, which greatly reduces pancreatic exocrine and the release and spread of platelet actived factors and improves microcirculation,

thus regulating cytokines to promote growth [8, 10]. Ulinastatin can suppress hydrolysis and activity of various proteases including trypsin, fibrinolytic enzyme, amylase and lipase, reduce the number of endogenous shock factors and inflammatory mediators, stop the activation of WBCs and lower the absorption of rnterogenic toxin, thus protecting multiple organ system from damage [11, 12].

Inhibiting activation and release of pancreatin and controlling inflammatory function and normal microcirculation are of great significance for the prognosis of SAP. Therefore, this study intended to explore the clinical efficacy of ulinastatin combined with somatostatin in the treatment of SAP and its effects on immune function.

Materials and methods

General materials

From Sep 2016 to Jul 2018, 82 patients with SAP admitted to Weihai Central Hospital were selected and were randomly divided into the control (n=41) and observation group (n=41). The control group was treated with conventional therapy, the observation group was treated with somatostatin and ulinastatin in addition to the conventional therapy of control group. There were 53 males and 29 females with an average age of (46.10±5.43) years. The patients' origin of the disease was for cholangitis-originating reason (31 patients), alcohol (24 patients), excessive food intake (17 patients), surgery (9 patients) and other (1 patient).

Inclusion and exclusion criteria

Patients meeting the SAP diagnostic criteria were included, and the following patients were excluded: Patients with acute gastric ulcer, combined hepatic renal dysfunction, respiratory disease, cognition disorders or communication obstacles, poor compliance and those having received antibiotic therapy recently. All patients and their families agreed to participate in the experiment and signed an informed consent form, and the experiment was approved by the Weihai Central Hospital Ethics Committee.

Experiment reagents and materials

Ulinastatin (purchased from Guangdong Techpool Bio-Pharma Co., Ltd., State Food and Drug Administration (SFDA) number: H19990134); somatostatin (purchased from Wuhan Hualong Bio-pharmaceutical Co., Ltd., SFDA number: H20059187); 5% glucose injection (purchased from Sichuan Kelun Pharmaceutical Co., Ltd.; SFDA number: H51020635); CD4+ and CD8+ monoclonal antibody (purchased from Santa Cruz Biological Technology Co., Ltd.); flow cytometry (purchased from Shanghai Shucheng Medical Technology Development Co., Ltd.); immune turbidimetry (purchased from Ampang (Xiamen) Biotechnology Co., Ltd.) and enzyme-linked immunosorbent assay (ELISA) kit (purchased from Beijing WDWK Biotechnology Co., Ltd.).

Experimental methods

Drug experiment: Both of the groups were treated with routine therapy for inflammation and infection, lower pancreatitis secretion and provide nutritional support while fasting for 2 weeks. The observation group was additionally treated with ulinastatin and somatostatin through intravenous drip (20 U of ulinastatin + 250 ml of glucose injection, and 3 mg of somatostatin + 25 ml of normal saline) at 1 ml/h, 2 times/d.

Determination method of immune cell levels in peripheral blood: Peripheral venous blood (3 ml) was taken from patients in the two groups before and after treatment, respectively, added with 50 μl of anticoagulant, and CD4+ and CD8+ monoclonal antibody and mixed. Then CD4+ and CD8+ lymphocytes were detected using flow cytometry and the number was analyzed with software, and IgG, IgA and IgM levels were detected using immune turbidimetry. All operation procedures were performed in strict accordance with product specifications.

Observation indexes

Statistics was performed on the following aspects of the two groups: Movement of laboratory indexes, intestinal function recovery, occurrence of complications, efficacy, cellular immune CD4+, CD8+ and CD4+/CD8+ levels, and IgA, IgM and IgG levels before and after treatment.

Statistical analysis

In the experiment, SPSS19.0 software (Beijing NDTimes Technology Co., Ltd.) was adopted for statistical analysis of experiment data. Count data were analyzed using chi-square test, and measurement data were showed in mean ±

Table 1. Comparison in general clinical data

Group	Control group n=41	Observation group n=41	t/x^2	P
Gender (person)			0.480	0.488
Male	25 (60.98)	28 (68.29)		
Female	16 (39.02)	13 (31.71)		
Age (year)	46.23±5.14	45.92±5.23	0.271	0.787
BMI	22.32±2.31	21.93±2.28	0.769	0.444
Causes			1.673	0.796
cholangitis-originated reason	16 (39.02)	15 (36.59)		
Alcohol	12 (29.27)	12 (29.27)		
Excessive food intake	7 (17.07)	10 (24.39)		
Surgery	5 (12.20)	4 (9.76)		
other	1 (2.44)	0		
Comorbidity			0.452	0.798
Biliary disease	16 (39.02)	18 (43.90)		
Abdominal hypertension	20 (48.78)	17 (41.46)		
other	5 (12.20)	6 (14.63)		
Body temperature (°C)	38.32±0.73	38.13±0.78	1.139	0.258
WBC (10^9/L)	16.42±4.24	16.46±4.28	0.043	0.966
CRP (mg/L)	98.43±33.85	97.58±34.54	0.113	0.911
AMS (U/L)	835.49±345.65	839.53±341.45	0.053	0.958
TBIL (μmol/L)	78.94±34.54	80.26±36.82	0.167	0.868
ALT (U/L)	194.73±87.49	191.49±82.49	0.173	0.864

Table 2. Comparison between the two groups in movement of laboratory indexes before and after treatment

Laboratory indicators	Control group n=41	Observation group n=41		
WBC (×10^9/L)				
Before treatment	16.42±4.24	16.46±4.28	0.043	0.966
After treatment	14.67±3.14*	11.36±3.13*	4.780	<0.001
CRP (mg/L)				
Before treatment	98.43±33.85	97.58±34.54	0.113	0.911
After treatment	84.74±36.93*	43.14±23.61*	6.077	<0.001
AMS (U/L)				
Before treatment	835.49±345.65	839.53±341.45	0.053	0.958
After treatment	507.45±121.46*	256.44±111.82*	9.735	<0.001
TBIL (μmol/L)				
Before treatment	78.94±34.54	80.26±36.82	0.167	0.868
After treatment	63.52±34.82*	47.22±26.67*	2.380	0.020
ALT (U/L)				
Before treatment	194.73±87.49	191.49±82.49	0.173	0.864
After treatment	142.27±47.67*	108.39±28.72*	3.898	<0.001

Note: in comparison with the situation before treatment, *P<0.05.

standard deviation. Comparison between the two groups was carried out with independent t test, and figures of the experiment were drawn using Graphpad Prism8. P<0.05 indicated statistical significance.

Results

Comparison in general clinical data

There was no significant difference in gender, age, BMI, cause of disease and complications between the two groups before treatment (all P>0.05) More details are shown in **Table 1**.

Comparison between the two groups in movement of laboratory indexes before and after treatment

The two groups were compared in laboratory indexes including WBC, CRP, AMS, TBIL and ALT, and the results revealed that both of the two groups showed a significant decrease in those indexes (all P<0.05), The laboratory indexes of the observation group were significantly lower than the control group (P<0.05). More details are shown in **Table 2**.

Table 3. Comparison between the two groups in intestinal function recovery after treatment

Group	Control group n=41	Observation group n=41	t	P
Duration for disappearance of abdominal pain	5.43±1.23	3.85±1.03	6.306	<0.001
Temperature recovery time	7.18±2.28	6.19±2.10	2.045	0.044
Time of abdominal distention recovering to normal	5.25±0.88	3.92±0.67	7.700	<0.001
Time of nausea and vomiting recovering to normal	4.87±1.33	3.78±1.18	3.925	<0.001
Time of upper abdominal pain recovering normal	7.32±1.78	6.26±1.46	2.948	0.004

Table 4. Comparison between the two groups in occurrence of complications

Group	Respiratory distress syndrome	Renal failure	Heart failure	Septicemia	Shock	Complication rate
Control group n=41	5 (12.20)	4 (9.76)	5 (12.20)	4 (9.76)	6 (14.63)	24 (58.54)
Observation group n=41	1 (2.44)	1 (2.44)	0	1 (2.44)	1 (2.44)	4 (9.56)
x^2	-	-	-	-	-	21.691
P	-	-	-	-	-	<0.001

Table 5. Comparison between the two groups in effective rate of treatment

Group	Cure	Significant effect	Effective	Invalid	Total efficiency
Control group n=41	11 (26.83)	10 (24.39)	13 (31.71)	7 (17.03)	34 (82.93)
Observation group n=41	16 (39.02)	15 (36.59)	9 (21.95)	1 (2.44)	40 (97.56)
x^2	-	-	-	-	4.986
P	-	-	-	-	0.026

Comparison between the two groups in intestinal function recovery after treatment

The observation group experienced significantly shorter duration for the disappearance of abdominal pain, temperature recovery time, time of abdominal distention, nausea and vomiting, and upper abdominal pain recovering to normal (all P<0.05). More details are shown in **Table 3**.

Comparison between the two groups in occurrence of complications

The complication rates of the control group and the observation group were 58.54% (24 patients) and 9.56% (4 patients), so the control group showed a significantly higher complication rate than the observation group (P<0.05). More details are shown in **Table 4**.

Comparison between the two groups in effective rate of treatment

The effective rates of treatment of the control group and the observation group were 82.93% (34 patients) and 97.56% (40 patients), so the control group showed a significantly lower effective rate of treatment than the observation group (P<0.05). More details are shown in **Table 5**.

Comparison between the two groups in cellular immune CD4+, CD8+ and CD4+/CD8+ levels

The comparison between the two groups in CD4+, CD8+ and CD4+/CD8 levels revealed that the control group showed significantly higher CD4+, CD8+ and CD4+/CD8 levels than the control group (all P<0.05). More details are shown in **Table 6** and **Figures 1** and **2**.

Comparison between the two groups in IgA, IgM and IgG levels before and after treatment

Before treatment, the control group showed no difference with the observation group in IgA, IgM and IgG levels (all P>0.05). After treatment, the control group still showed no significant difference with the observation group in IgA and IgM levels (both P>0.05), but showed significantly lower IgG level than the observation group (P<0.05). More details are shown in **Table 7** and **Figure 3**.

Table 6. Comparison between the two groups in cellular immune CD4+, CD8+ and CD4+/CD8+ levels

Group	Control group n=41	Observation group n=41	t	P
CD4+ (%)	35.42±2.13	21.42±1.23	36.450	<0.001
CD8+ (%)	29.48±1.18	22.43±0.87	30.790	<0.001
CD4+/CD8+	1.72±0.28	1.24±0.16	9.531	<0.001

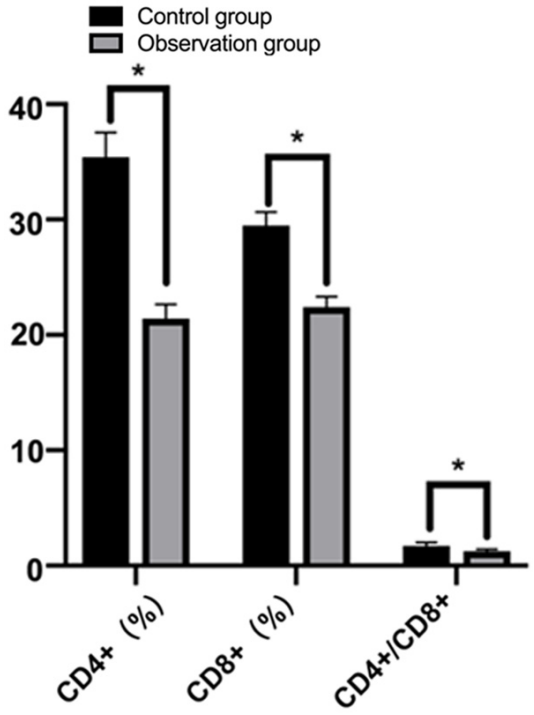

Figure 1. Comparison between the two groups in cellular immune CD4+, CD8+ and CD4+/CD8+ levels. The control group showed significantly higher CD4+, CD8+ and CD4+/CD8 levels than the observation group (all P<0.05). Note: *P<0.05.

Discussion

Caused by a variety of pathogenic factors, SAP can be a vicious cycle as follows: pancreatic acini is seriously damaged and massive pancreatin is activated and released, then the pancreas performs autolysis by damaging adipocytes and glyceryl phosphatide in the mitochondrial membrane, this decomposes lyceryl phosphatide into lysolecithin and activates mononuclear, macrophages and neutrophils, leading to excessive release of inflammatory factors, and then with the progression of SAP, the pancreas itself and para-pancreatic tissues gradually become necrotic, causing acute systemic inflammatory responses and multiple organ injuries with toxic substances absorbed into blood [13, 14]. In addition, the key for the onset of SAP is over-activation of pancreatin, so timely and effective inhibition of pancreatin secretion and inflammation resistance are key to saving patients and improving prognosis. Somatostatin, as a highly effective and widely used neurotrypsin inhibitor, can stabilize lysosome membrane, suppress pituitary growth hormone and production and release of pituitary hormone for stimulation by adenohypophysis, block interaction between inflammatory transmitters and WBC, relieve the damage from WBC to tissues and cut off the development of inflammatory lesions, thus protecting the normal function of organs [15, 16]. Ulinastatin, as a protease inhibitor, can stabilize proplasmin release and decomposition, inhibit pancreatin secretion, loose circular sphincter and suppress the release of inflammatory mediators by cleaning up oxygen free radicals, thus accelerating the proliferation and repair of pancreatic cells [17, 18].

The results of our study revealed that the observation group and the control group showed significantly decreased laboratory indexes after treatment (all P<0.05) and the observation group showed a more significant decrease than the control group (P<0.05), which suggested that ulinastatin and somatostatin can treat SAP in a mutually assisted manner, and can significantly suppress the expression of inflammatory factors and up regulate AMS and TBIL levels. The laboratory indexes for this study were generally picked out from indexes available to determine acute pancreatitis. Previous studies have confirmed that pathogen stimulation is the fuse for a series of cascade reactions of AMS, TBIL and others cytokines. AMS and TBIL are highly expressed in SAP patients' serum and can be used to detect tissue damage and inflammatory responses [19, 20]. Previous studies have also confirmed that cytokines such as CRP are independent risk factors for SAP, and the increase of related inflammatory factors can aggravate and damage pancreatic tissue of patients [21]. Our study revealed that with ulinastatin and somatostatin, laboratory indexes decreased, which indicated that ulinastatin combined with somatostatin can suppress the inflammatory response, which corresponds to the conclusion in other studies. After

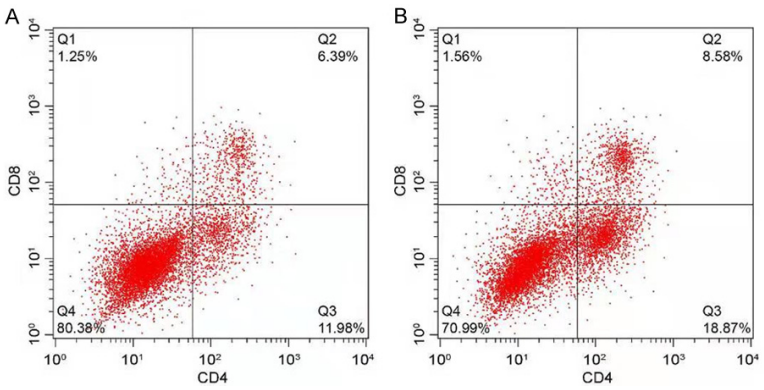

Figure 2. Flow cytometry of CD4+ and CD8+ in the two groups of patients after treatment. Flow cytometry of CD4+ and CD8+ in two groups of patients after treatment in observation group (A) and control group (B).

Table 7. Comparison between the two groups in IgA, IgM and IgG levels before and after treatment (g/L)

Group	Control group n=41	Observation group n=41	t	P
Before treatment IgA	4.32±1.03	4.31±1.02	0.044	0.965
After treatment IgA	5.21±1.13*	5.22±1.14*	0.040	0.968
Before treatment IgM	1.02±0.19	1.01±0.17	0.251	0.802
After treatment IgM	1.18±0.24*	1.17±0.22*	0.197	0.845
Before treatment IgG	10.83±1.84	10.84±1.85	0.025	0.981
After treatment IgG	15.71±2.23*	19.26±2.16*	7.322	<0.001

Note: in comparison with situation before treatment, *P<0.05.

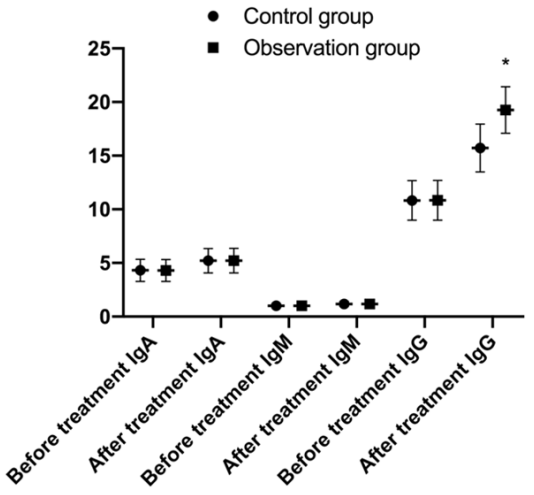

Figure 3. Comparison between the two groups in IgA, IgM and IgG levels before and after treatment (g/L). Before treatment, the control group showed no difference with the observation group in IgA, IgM and IgG levels (all P>0.05); after treatment, the control group still showed no significant difference with the observation group in IgA and IgM levels (both P>0.05), but showed significantly lower IgG level than the observation group (P<0.05). Note: In comparison with the situation before surgery, *P<0.05.

treatment, the observation group experienced a significantly shorter duration for the disappearance of abdominal pain, temperature recovery time, time of abdominal distention, nausea and vomiting, and upper abdominal pain recovering to normal, over the control group (all P<0.05). Higher complication rates in control group was significant over that in the observation group (P<0.05), which indicated that ulinastatin combined with somatostatin in the treatment of SAP can improve the recovery rate of patients, shorten the time of clinical symptoms recovering to normal and provide relatively high drug safety. Previous studies have shown that somatostatin has significant effects on lowering the mortality rate of SAP patients, but cannot control the incidence of adverse reactions to an ideal level, and relevant scholars have confirmed that with significant effects on lowering the incidence of adverse reactions of pancreatitis, ulinastatin can remedy the weakness of somatostatin alone in the incidence of adverse reactions when being used with somatostatin [22, 23]. The effective rate of treatment for the control group was significantly lower than that for the observation group (P<0.05), which suggested that combination of ulinastatin and somatostatin can significantly improve the total effective rate in treatment of SAP. It directly verifies the trustworthiness and reliability of our study.

In terms of immune function, the control group showed significantly higher CD4+, CD8+ and CD4+/CD8+ levels than the observation group (all P<0.05), and after treatment, the control group showed no significant difference with the observation group in IgA and IgM levels (both P>0.05), but showed significantly lower IgG level than the observation group (P<0.05), which indicated that SAP patients themselves have their own immune suppression effect and ulinastatin combined with somatostatin can strengthen body immunity. Ulinastatin com-

bined with somatostatin affects mitosis of T cells during treatment, and CD4+T cells and CD8+T cells are T lymphocytes involved in the cellular immune response [24-26]. Acute inflammation causes immune dysfunction and suppresses the function of lymphocytes including B cells, and immunoglobulin synthesis will decrease for autoantibody hyposecretion with decrease of B cell function and IgG, IgM, and IgA levels in peripheral blood will decrease accordingly [27]. Regulation of T cells in the above references is consistent with our study, but in terms of immunoglobulin, only the regulation of IgG is consistent with our study. It is inferred that IgA and IgM expression is different in different stages of the inflammatory response. All the above studies and our results indicated that ulinastatin combined with somatostatin regulates partial immune response during treatment by strengthening the bodies' immunological resistance and helping to recover the immune response level.

In summary, for SAP patients, both ulinastatin and somatostatin are effective in treatment of SAP, because they can significantly inhibit the inflammatory response, down regulate the expression of predictable inflammatory response factors in serum, enhance immune function, and ulinastatin combined with somatostatin can treat SAP in a targeted way with better efficacy. However, there are also some shortcomings of our study. For example, the difference of clinical efficacy between the two separate drugs and the two drugs combined were not compared. It is this research direction we will pay attention to and explore, and it is also expected that other scholars will pay attention to and explore it.

Disclosure of conflict of interest

None.

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