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Original Article

Effect of Xuebijing combined with ulinastatin on inflammatory factors and gastrointestinal function in severe acute pancreatitis

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Abstract: Objective: This study was designed to probe into the efficacy of Xuebijing (XBJ) combined with ulinastatin on severe acute pancreatitis (SAP) and its influence on inflammatory factors and gastrointestinal function. Methods: A total of 182 patients with SAP who were treated in the Emergency Department of our hospital from October 2017 to November 2018 were selected as the research subjects. From which, 76 treated who were with ulinastatin alone were considered as the monotherapy group (MG) and 64 treated by XBJ combined with ulinastatin were regarded as the combined group (CG). The clinical efficacy, time of clinical symptoms disappearance and hospitalization, complications and adverse reactions were compared between the two groups after treatment, and the levels of gastrointestinal hormones and inflammatory cytokines in serum were detected before and after treatment. Results: Compared with the MG, the CG had better clinical effective rate, shorter time of disappearance of clinical symptoms and hospitalization, and lower incidence of complications ($P < 0.05$). There were no serious adverse reactions in both groups, and there was no marked difference in the incidence of adverse reactions ($P > 0.05$). After treatment, the levels of gastrin (GAS) and motilin (MTL) in the two groups decreased markedly, while the levels of vasoactive intestinal peptide (VIP) increased remarkably ($P < 0.05$). The levels of GAS and VIP in the combined group were lower than those in the single drug group, while the MTL level was higher ($P < 0.05$). After treatment, the levels of hs-CRP, TNF-α and IL-8 decreased markedly in both groups, and the three indexes of the combined group were lower than those of the single drug group ($P < 0.05$). Conclusion: XBJ combined with ulinastatin is effective in treating patients with SAP, which can improve gastrointestinal function, reduce inflammation and complications, and as such it worthy to be popularized.

Keywords: Severe acute pancreatitis (SAP), gastrointestinal function, Xuebijing, ulinastatin

Introduction

Acute pancreatitis (AP) is a disease that is characterized by acute necrotizing inflammation of pancreas, and is a common cause of intestinal related hospitalization [1]. According to reports, the annual morbidity of AP ranges from 15.9 to 36.4 per 100,000 people, its prevalence is still increasing, and it seriously threatens the life and health of patients [2]. Most patients with AP have mild symptoms that can be cured by symptomatic treatment, but about 20% to 30% will develop into severe AP (SAP) and can be life threatening [3]. At present, SAP is mainly treated by anti-infection drugs, nutritional support and correction of water and electrolyte imbalance. Although this can alleviate patients' illness to a certain extent, their prognosis is still very poor [4, 5]. Therefore, it is important to explore more effective treatment schemes.

Xuebijing (XBJ) is a Chinese medicine composed of extracts of Chinese herbal medicines such as safflower, red peony root, Ligusticum wallichii, Salvia miltiorrhiza and Angelica sinensis, which can antagonize endotoxins, inhibit the release of inflammatory mediators, prevent oxidative stress and improve microcirculation [6, 7]. Previous studies have shown that XBJ can treat SAP safely and effectively [8]. Ulinastatin is a glycoprotein extracted from human urine, which can inhibit the activity of many proteolytic enzymes. It is mainly used to treat AP, chronic recurrent pancreatitis and acute circulatory failure [9]. A previous meta-analysis reported that compared with ulina-

statin alone, XBJ combined with ulinastatin was more effective in treating septicemia, and its safety was within an acceptable range [10]. This indicates that XBJ combined with ulinastatin may also be safe and effective for SAP. However, there are few clinical reports on this combination therapy.

This study will explore the efficacy and safety of XBJ combined with ulinastatin in treating SAP, aiming at finding a safer and more effective treatment schemes. The results revealed that compared with ulinastatin alone, XBJ combined with ulinastatin could provide better clinical efficacy, shorter disappearance time of clinical symptoms, shorter hospitalization time and lower complications for SAP patients, and could also promote the recovery of gastrointestinal function and reduce the inflammatory reaction of the body more effectively. In addition, it does not produce adverse reactions that are unacceptable to people.

Research subjects and treatment

Sources of research subjectse

A total of 182 SAP patients treated in the Emergency Department of Huangdao district Chinese Medicine Hospital from October 2017 to November 2018 were selected as the research subjects. From which, 76 patients treated with ulinastatin alone were considered as the monotherapy group (MG) and 64 patients treated by XBJ combined with ulinastatin were regarded as the combined group (CG). Inclusion criteria: those were in line with the diagnostic criteria of SAP [11]; 18-65 years old. Exclusion criteria: who those took anti-inflammatory or pancreatic enzyme secretion inhibiting drugs in the past month; those who had incomplete clinical data; those who had severe heart, liver and kidney dysfunction; people who were allergic to the drugs used; those who had poor treatment compliance or could not communicate normally; and pregnant women. All patients signed an informed consent form, and this study was approved by the Ethics Committee of our hospital.

Treatment

MG: After admission, patients were given routine treatment such as gastrointestinal decompression, anti-infection drugs, they fasted, were assisted with correction of water and electrolyte imbalance, and given nutritional support. On this basis, ulinastatin (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., SFDA Approval No. H19990133) at 100,000 units was injected intravenously every 12 h for 7 days. CG: Patients received ulinastatin equal to the MG and XBJ (Tianjin Chase Sun Pharmaceutical Co., Ltd., SFDA Approval No. Z2004-0033) was added with 100 ml diluted in 100 ml saline for an intravenous drip, twice a day, for 7 days. The recovery of clinical symptoms after treatment was recorded.

Outcome measures

The evaluation criteria of clinical efficacy: markedly effective: seven days after treatment, the clinical symptoms (fever, abdominal pain, abdominal distension, nausea and vomiting) disappeared, and the laboratory indexes (blood amylase, urine amylase and white blood cell count) also returned to normal. Effective: seven days after treatment, the clinical symptoms and laboratory examination indexes improved. Ineffective: seven days after treatment, the condition did not improve or even worsened. Total effective rate = (markedly effective + effective)/total cases × 100%.

The complications and drug side effects of the two groups during hospitalization were recorded. The former mainly included renal failure, shock, heart failure, pancreatic pseudocyst and gastrointestinal injury, and the latter mainly included skin itching, nausea and vomiting, dizziness and headache, diarrhea and granulocytopenia.

Before and 7 days after treatment, 5 mL fasting venous blood was taken from both groups and centrifuged (4C, 1500 × g, 10 min) to collect serum. The levels of inflammatory factors in serum were detected by ELISA, including high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8). The levels of gastrin (GAS), motilin (MTL) and vasoactive intestinal peptide (VIP) in serum samples were detected by radioimmunoassay.

Statistical processing

Statistical analysis was performed with SPSS 21.0 (IBM Corp, Armonk, NY, USA), and data was illustrated with GraphPad Prism 7. The

Table 1. Comparison of general data between both groups ($\bar{x} \pm sd$), [n (%)]

Group	Monotherapy group (n = 76)	Combined group (n = 64)	χ^2/t	P
Age (years)	45.18±6.85	46.29±6.01	0.314	0.626
BMI (kg/m^2)	23.41±1.45	23.36±1.32	0.212	0.833
Course of disease (h)	13.21±5.15	12.55±4.72	0.785	0.434
APACHE II score	12.05±1.72	12.43±1.86	1.255	0.212
Gender			1.740	0.187
Male	51 (67.11)	36 (56.25)		
Female	25 (32.89)	28 (43.75)		
History of smoking			0.979	0.323
Yes	42 (55.26)	30 (46.88)		
No	34 (44.74)	34 (53.12)		
Alcoholism			0.359	0.549
Yes	58 (76.32)	46 (71.88)		
No	18 (23.68)	18 (28.12)		

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

Group	Markedly effective	Effective	Ineffective	Total effective rate
Monotherapy group (n = 76)	46 (60.53)	16 (21.05)	14 (18.42)	62 (81.58)
Combined group (n = 64)	48 (75.00)	12 (18.75)	4 (6.25)	60 (93.75)
χ^2	-	-	-	4.594
P	-	-	-	0.032

Table 3. Comparison of time of remission and hospitalization of clinical symptoms between both groups after treatment ($\bar{x} \pm sd$)

Group	Monotherapy group (n = 76)	Combined group (n = 64)	t	P
Exhaust (h)	26.56±7.75	14.56±6.98	9.547	< 0.001
Defecation (h)	33.82±6.23	24.45±5.93	9.062	< 0.001
Bowel sounds (d)	4.47±1.85	3.05±1.56	4.856	< 0.001
Abdominal distension (d)	5.56±1.22	4.15±1.33	6.537	< 0.001
Abdominal pain (d)	7.64±2.12	5.42±1.89	6.484	< 0.001
Length of stay (d)	14.15±3.25	10.72±3.61	5.913	< 0.001

counting data were compared through Chi-square test. The measurement data between the two groups were assessed by independent-samples t test, and the comparison before and after treatment in the same group was made by paired t-test, while those between multiple groups were compared by one-way ANOVA, and the correctness of the statistical values was verified by back testing. $P < 0.05$ indicated significant differences.

Results

Comparison of general data

There was no remarkable difference in age, BMI index, course of disease, APACHE II score, gender, smoking history, alcoholism and other general data between the two groups ($P > 0.05$), as shown in **Table 1**.

Comparison of clinical efficacy

After evaluating the clinical efficacy of both groups, we found that the treatment in 46 cases was markedly effective, 16 cases were effective and 14 cases were ineffective in the MG, with a total effective rate of 81.58%. While in the CG, the treatment in 48 cases was markedly effective, 12 cases were effective and 4 cases were ineffective, with a total effective rate of 93.75%. The total effective rate of the CG was higher than that of the MG ($P < 0.05$) (**Table 2**).

Comparison of time of symptom disappearance and hospitalization

By observing the disappearance time of the main clinical symptoms, we found that the disappearance time of the main symptoms such as exhaust, defecation, bowel sounds, abdominal distension and pain in the CG was shorter than that in the MG ($P < 0.05$). In addition, the hospitalization time in the CG was also shorter than that in the MG ($P < 0.05$) (**Table 3**).

Table 4. Comparison of complications [n (%)]

Group	Monotherapy group (n = 76)	Combined group (n = 64)	X^2	P
Renal failure	3 (5.26)	1 (1.56)	1.382	0.240
Shock	2 (2.63)	0 (0.00)	1.709	0.191
Heart failure	2 (2.63)	1 (1.56)	0.189	0.663
Pancreatic pseudocyst	5 (6.58)	3 (4.69)	0.231	0.631
Gastrointestinal injury	9 (11.84)	3 (3.13)	3.647	0.056
Total complications	21 (27.63)	7 (10.94)	6.052	0.014

Comparison of complications

After recording the complications of the two groups during hospitalization, we found that there were 3 cases of renal failure, 2 cases of shock, 2 cases of heart failure, 5 cases of pancreatic pseudocyst and 9 cases of gastrointestinal injury in the MG, with a total complication rate of 27.63%. There was 1 case of renal failure, 1 case of heart failure, 3 cases of pancreatic pseudocyst and 3 cases of gastrointestinal injury in the CG, and the total complication rate was 10.94%. The total complication rate of the CG was lower than that of the MG ($P < 0.05$) (**Table 4**).

Comparison of gastrointestinal hormone levels

We tested serum gastrointestinal hormone levels of patients in both groups, and found that there was no obvious difference in the levels of GAS, VIP and MTL before treatment ($P > 0.05$). After treatment, the levels of GAS and VIP in the two groups decreased markedly, while the MTL levels increased markedly ($P < 0.05$). The levels of GAS and VIP in the combined group were lower than those in the single drug group, while the MTL levels in the combined group was higher ($P < 0.05$) (**Figure 1**).

Comparison of inflammatory factors

We detected serum levels of inflammatory factors of patients in both groups, and found that before treatment, there was no marked difference in the levels of hs-CRP, TNF-α and IL-8 ($P > 0.05$). After treatment, the hs-CRP, TNF-α and IL-8 levels in the two groups decreased markedly, and the three indexes of the combined group were lower than those of the single drug group ($P < 0.05$) (**Figure 2**).

Comparison of adverse reactions

Patients in both groups had some adverse reactions after medication, but there were no adverse reactions that endangered their lives or were difficult to cure. In the single drug group, itchy skin occurred in 2 cases (2.63%), nausea and vomiting in 3 (3.95%), dizziness and headache in 2 cases (2.63%), diarrhea in 2 cases (2.63%), granulocytopenia in 3 cases (3.95%), and the total incidence of adverse reactions was 15.79%. In the combined group, itchy skin occurred in 4 cases (6.25%), nausea and vomiting in 5 (7.81%), dizziness and headache in 2 cases (3.13%), diarrhea in 3 cases (4.69%), granulocytopenia in 4 cases (6.25%), and the total incidence of adverse reactions was 28.13%. There was no remarkable difference in the incidence of adverse reactions between the two groups ($P > 0.05$) (**Table 5**).

Discussion

SAP is a common clinical critical acute abdominal disease, which has complex conditions, rapid progress and poor prognosis [12]. At present, there are many schemes to treat SAP, but the prognosis is still very poor [13]. Thus, it is urgent to explore treatment schemes that can improve the prognosis of patients. Ulinastatin is a trypsin inhibitor, which can reduce pancreatic self-digestion and endotoxin absorption and inhibit the release of inflammatory factors, and it is often used for SAP treatment [14, 15]. XBJ is a Chinese medicine made from a variety of Chinese herbal medicines, which has been used in clinical practice in China for more than ten years [16], and can be used to treat various diseases including AP. Although both ulinastatin and XBJ can effectively treat SAP, we still don't know whether the combination therapy can provide better efficacy for patients. In this study, XBJ and ulinastatin were combined to treat SAP. The results revealed that the total effective rate of treatment in the CG was higher than that in the MG, and the disappearance time of clinical symptoms and hospitalization time were shorter than those in the MG. Besides, the incidence of complications in the CG was lower than that in the MG. Subsequently, we recorded the incidence of adverse reactions in both groups, and found that there were no adverse reactions that endangered patients' lives and were difficult to cure, and the incidence in both groups was similar. This shows that XBJ combined with ulinastatin is effective and safe.

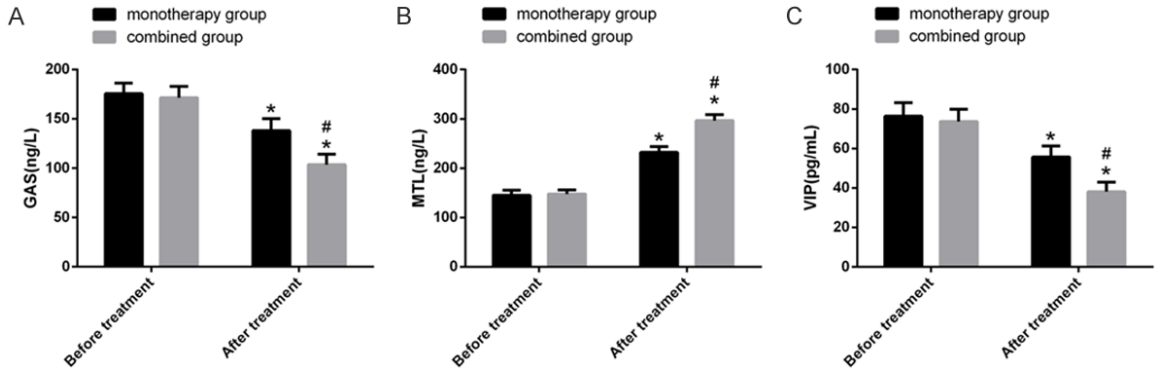

Figure 1. Comparison of gastrointestinal hormone levels. A. Comparison of GAS changes between both groups before and after treatment; B. Comparison of MTL changes between both groups before and after treatment; C. Comparison of VIP changes between both groups before and after treatment. Note: *represents the comparison between the same group and before treatment ($P < 0.05$); #represents the comparison with MG after treatment ($P < 0.05$).

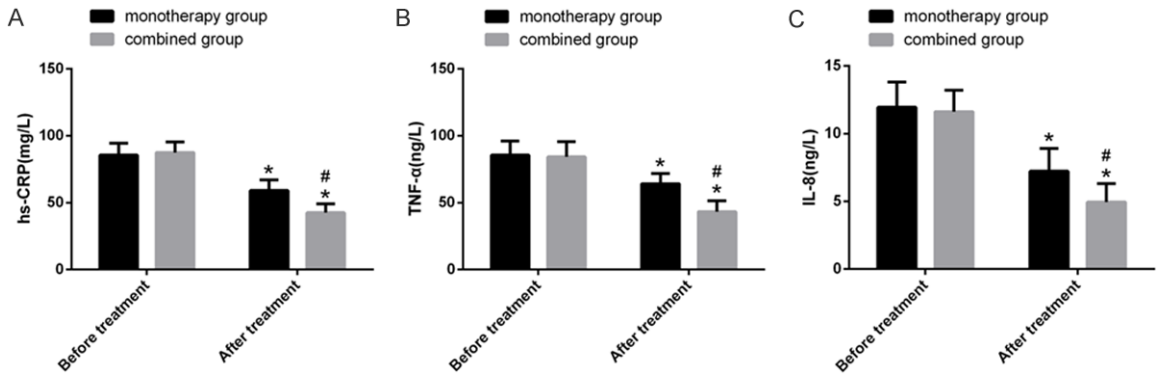

Figure 2. Comparison of inflammatory indicators. A. Comparison of hs-CRP changes between both groups before and after treatment; B. Comparison of changes of TNF-α between both groups before and after treatment; C. Comparison of IL-8 changes between both groups before and after treatment. Note: *represents the comparison between the same group and before treatment ($P < 0.05$); #represents the comparison with MG after treatment ($P < 0.05$).

Table 5. Incidence of adverse reactions [n (%)]

Group	Monotherapy group (n = 76)	Combined group (n = 64)	χ^2	P
Itchy skin	2 (2.63)	4 (6.25)	1.109	0.292
Nausea and vomiting	3 (3.95)	5 (7.81)	0.963	0.326
Dizziness and headache	2 (2.63)	2 (3.13)	0.030	0.861
Diarrhea	2 (2.63)	3 (4.69)	0.426	0.514
Granulocytopenia	3 (3.95)	4 (6.25)	0.388	0.534
Total adverse reactions	12 (15.79)	18 (28.13)	3.140	0.076

The gastrointestinal tract is a reservoir of whole body flora, which regulates immunity and inflammation. However, SAP will destroy the barrier of gastrointestinal mucosa and increase the permeability of gastrointestinal tract, thus leading to the shift of enteric bacteria and toxin, bringing about endogenous infections and a systemic inflammatory response syndrome in patients, and can even result in multiple organ failure in severe cases [17, 18]. A recent study has shown that once acute gastrointestinal injury occurs in SAP patients, the mortality and complication rates will increase markedly [19]. Hence, active treatment of acute gastrointestinal injury and promotion of gastrointestinal function recovery are keys to alleviate the condition and prognosis of SAP patients [20, 21]. GAS, MTL and VIP are all important hormones that regulate gastrointestinal function, which shows abnormal expression in AP patients [22]. After treatment, the GAS and VIP levels decreased markedly, while the MTL lev-

els increased obviously; the levels in the CG were lower than those in the MG, while the MTL levels were higher than those in the MG. Therefore, XBJ combined with ulinastatin can effectively regulate the secretion of GAS, MTL, VIP and other hormones, and promote the early recovery of gastrointestinal function. The activation of a systemic inflammatory reaction is a key pathological link that causes SAP development and progression. Inflammatory reactions will lead to a large release of inflammatory factors, which is the main cause of tissue injury and local injury aggravation [23, 24]. hs-CRP, TNF-α and IL-8 are commonly used to reflect the severity of the inflammatory reaction. This study revealed that the levels of the three inflammatory indicators in the two groups decreased remarkably after treatment, and these indexes in the CG were all lower than those in the MG. This indicates that XBJ combined with ulinastatin can also reduce the inflammatory reaction of SAP patients effectively.

The above results reveal that compared with ulinastatin alone, XBJ combined with ulinastatin can provide better clinical treatment effect for SAP patients. The reason is that XBJ and ulinastatin have different mechanisms for treating SAP that do not interfere with each other, and they play their own therapeutic roles effectively, thus achieving better efficacy. What's more, XBJ has many therapeutic effects, especially the effects of antagonizing endotoxins, inhibiting the release of inflammatory mediators and improving microcirculation [6, 7], which can all help patients control the disease development in many ways.

There are some shortcomings in this study, such as: (1) The effect and safety of XBJ combined with ulinastatin on people outside the age range of 18-65 years old were not explored. (2) The best compatible dose of XBJ combined with ulinastatin in treating SAP was not explored, and the treatment cost brought by the two treatment methods was not compared. We hope these can be investigated in future research.

Stated thus, XBJ combined with ulinastatin is effective in treating SAP patients, which can improve gastrointestinal function, reduce inflammatory reactions and complications effectively, and are worthy of being popularized.

Disclosure of conflict of interest

None.

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