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• *BRIEF REPORTS* •

Comparison of integrated Chinese and Western medicine with and without somatostatin supplement in the treatment of severe acute pancreatitis

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Abstract

AIM: To evaluate the therapeutic effect of the combined use of early short-term somatostatin and conventional integrated Chinese and Western medicine in treating severe acute pancreatitis.

METHODS: Sixty patients with severe acute pancreatitis were divided at random into a somatostatin group and a basic treatment group. Both groups received integrated traditional Chinese and Western medicine without surgery. For patients in the somatostatin group, somatostatin was infused intravenously 250 μg/h for 72 h; other medications were the same as in the basic treatment group. In both groups, comparisons of therapeutic effectiveness were made in terms of morbidity of organic dysfunction and mortality rate, and severity of the disease according to serum levels of C-reaction protein, scores of acute physiology and chronic health evaluation (APACHE II), and scores of Balthazar-CT.

RESULTS: The indexes for C-reaction protein levels on the fourth and seventh days, and APACHE II scores on the seventh day after treatment, were significantly improved in the somatostatin group than in the basic treatment group. The morbidity of organic dysfunction was lower in the somatostatin group than in the basic treatment group, although the difference was not statistically significant. There was no significant difference in mortality between the two groups.

CONCLUSION: We conclude that combined traditional Chinese and Western medicines with an early short-term use of somatostatin can improve the condition of patients with severe acute pancreatitis.

Key words: Severe acute pancreatitis; Somatostatin supplement; C-reaction protein level; APACHE II; Balthazar-CT

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INTRODUCTION

Somatostatin is a strong inhibitor of pancreatic secretion. Since the 1980 s, somatostatin has been used to treat pancreatitis and complications resulting from surgery for pancreatitis, and has achieved good results. In the treatment of severe acute pancreatitis, we have also obtained good results with combined traditional Chinese and Western medicines without the use of somatostatin[1]. However, the effective ingredients of Chinese medicines used by us do not directly inhibit external secretion of the pancreas. Therefore, this study was undertaken to evaluate the effects of early short-term treatment with somatostatin, combined with traditional Chinese and Western medicines, in cases of severe acute pancreatitis.

MATERIALS AND METHODS

Inclusion criteria

(1) Confirmed diagnosis of severe acute pancreatitis and scores of APACHE II[2] ⩾8. The diagnosis was made in accordance with the criteria in "Clinical Diagnosis of Acute Pancreatitis and Criteria for Grading" formulated by the Chinese Medical Association[3].

(2) Admission within 72 h of onset, and not treated with somatostatin or analogues before admission.

Exclusion criteria

(1) Mild cases of pancreatitis. (2) Admission after 72 h of onset, or presence of pancreatic pseudocyst or/and pancreatic abscess on admission, or surgery performed before admission. (3) Treated with somatostatin or analogues before admission. (4) Allergic to the medicine Stilamin. (5) Pregnant women, breast-feeding women, or patients with serious primary diseases of the heart, lung, liver, kidney or the hematopoietic system, or patients with mental disorders.

Patient data

Sixty consecutively-admitted patients were chosen according

to these criteria. Using the Random Number Table, they were divided into a somatostatin treatment group and a basic treatment group of 30 patients each. In the basic treatment group, there were 15 male and 15 female patients, ranging in age from 30 to 71 years, with an average age of 50. Their disease course was 53±15 h, and their APACHE II score was 14.10±4.30. There were 21 cases of type I and nine cases of type II. In the somatostatin treatment group, there were 14 male and 16 female patients, ranging in age from 33 to 70 years, with an average age of 48. Their disease course was 57±12 h; the APACHE II score was 13.80±4.50. There were 22 cases of type I and eight cases of type II. There was, thus, no statistically significant difference between the two groups ($P>0.05$).

Cases which had a definite cause numbered 23 in the basic treatment group and 19 in the somatostatin treatment group. In the former, 13 cases had biliary tract disease, five cases were alcoholic, four cases had hyperlipemia and one case had hypercalcemia. In the somatostatin treatment group, 11 cases had biliary tract disease, three cases were alcoholic, four cases had hyperlipemia and one had duodenal diverticulum. Again, there was no statistically significant difference between the groups ($P>0.05$).

In four cases in the basic treatment group and five in the somatostatin treatment group, definite necrosis of pancreas could be visualized on CT scan at admission, with a necrotic area of less than 30%. In this respect as well, there was no statistically significant difference between the two groups ($P>0.05$).

Treatment

The regimen of combined traditional Chinese medicine (TCM) and Western medicine was common to the treatment of both groups. Western medicine methods included fasting, gastrointestinal decompression, H_2 receptor blocking agent, water-electrolyte balance, homeostasis, symptomatic treatment, infection prevention, alimentotherapy, and organ function protection. TCM methods of treatment were based on differentiation of symptoms and signs according to the type of syndrome and the staging of severe acute pancreatitis in TCM. In the acute reaction stage (one week after onset), expelling stasis by purgation was the main method, supplemented with dispersing and rectifying the depressed liver-*qi*, purifying the pathogenic heat and removing toxic materials. In the infection stage (2-3 wk after onset), purifying the pathogenic heat and removing toxic materials, supplementing *qi* and bringing back *yin* were the main methods, supplemented with expelling stasis by purgation and activating the blood circulation to eliminate blood stasis. In the recovery stage (4 wk-2 mo after onset), invigorating *qi* and the blood, invigorating the spleen and eliminating wetness evil, and activating the blood circulation to eliminate blood stasis were used to regulate the whole body functions. The combined treatment of supplementing *qi* and bringing back *yin,* activating the blood circulation to eliminate blood stasis, purifying the pathogenic heat and removing toxic materials, and expelling stasis by purgation was called the therapy of "supplementing, activating, purifying, and expelling".

Four types of severe acute pancreatitis were found according to TCM: stagnation of the liver-*qi*, damp-heat in the liver and gallbladder, fever of excess type in the spleen and stomach, and upward intrusion of ascaris. The remedies used were respectively: Da Chai Hu Tang (decoction of Bupleuri for regulating Shaoyang Yangming); Da Chai Hu Tang combined with Long Dan Xie Gan Tang (decoction of Gentianae for purging liver-fire); Cai Qin Chen Qi Tang (decoction for purgation); and Da Chai Hu Tang combined with Wu Mei Tang (decoction of Mume). These were modified in the prescriptions at each stage. The decoctions could be given orally, by a stomach tube, or by enema. The average treatment course was one month.

While both groups received the combined treatment, somatostatin was used additionally for the somatostatin treatment group. Administration of the drug consisted of Stilamin 250 μg/h, infused intravenously for 72 h.

Observation and analysis methods

APACHE II scores and C-reaction protein levels were determined just before treatment and on the fourth and seventh days after treatment. APACHE II scores before treatment were used not only as an inclusion criterion but also as an index of the severity of the patient's condition.

Abdominal enhanced-CT scanning was performed on admission and 15 d after treatment and Balthazar[4] scores were also determined so as to assess and compare local damage to the pancreas.

Indexes of therapeutic effects included mortality in the early stage (occurring within one week of admission), overall mortality (occurring during the whole hospitalization), and morbidity of organic dysfunction according to guidelines described in literature[5].

Statistical analysis was made with software SPSS 10.0 for Windows.

RESULTS

Comparison of serum C-reaction protein levels

In both groups, serum C-reaction protein levels were high one day after admission, but significantly decreased on the fourth and seventh days after treatment ($P<0.05$). The decrease in serum C-reaction protein level was greater in the somatostatin treatment group than in the basic treatment group ($T = 2.56$, $T = 3.53$, respectively, $P<0.05$) (Table 1).

Table 1 Comparison of serum C-reaction protein levels between two groups (mg/L, mean±SD)

Group	d 1	d 4	d 7
Somatostatin	292±145	188±102[a,c]	118±62[a,c]
Basic treatment	287±152	234±110[c]	165±98[c]

[a]$P<0.05$ *vs* basic treatment group; [c]$P<0.05$ *vs* previous level.

Comparison of APACHE II scores

APACHE II scores decreased significantly after treatment in both groups ($P<0.05$), suggesting an improvement in the condition of patients. But the scores were lower in the somatostatin treatment group than in the basic treatment

group on the seventh day after treatment (T = 3.02, $P<0.05$) (Table 2).

Table 2 Comparison of APACHE II scores before and after treatment between two groups (mg/L, mean±SD)

Group	d 1	d 4	d 7
Somatostatin	13.80±4.50	10.54±3.36[c]	4.30±1.08[a,c]
Basic treatment	14.10±4.30	11.21±2.39[c]	6.21±2.39[c]

[a]$P<0.05$ *vs* basic treatment group; [c]$P<0.05$ *vs* previous score.

Comparison of Balthazar-CT scores

There were 28 cases in each group. In the somatostatin treatment group, the scores were 4.3±1.28 and 3.9±0.96 before and after treatment. In the basic treatment group, the scores were 4.5±1.13 and 4.1±1.05 respectively. The Balthazar-CT scores were lower after treatment in both groups, suggesting a reduction in inflammation of the pancreas or in local inflammation around the pancreas. But there was no statistically significant difference between the two groups before and after treatment ($P>0.05$).

Comparison of morbidity of organ dysfunction

There was no statistically significant difference between the two groups ($P>0.05$) (Table 3).

Table 3 Comparison of morbidity of organ dysfunction (episodes)

	Somatostatin group	Basic treatment group
Dysfunction of cardiovascular system	4	4
Dysfunction of lungs	7	8
Dysfunction of kidneys	2	3
Dysfunction of liver	0	2
Dysfunction of gastro-intestinal system	5	6
Septicemia	3	4

Comparison of mortality

Five deaths resulted from multiple organ failure one week after admission, with a mortality rate of 9%. Of these, three occurred in the somatostatin treatment group with an early mortality rate of 11%, and twoin the basic treatment group with an early mortality rate of 7%. There was no statistically significant difference between the two groups ($P>0.05$). A total of eight deaths occurred during the whole disease course in the two groups, with an overall mortality rate of 14%, - three in the somatostatin treatment group with a mortality rate of 11%, and five in the basic treatment group with a mortality rate of 17%. Of these, two died of pancreatic infection and one of septicemia. The mortality rate during the whole disease course was lower in the somatostatin group than in the basic treatment group, but the difference was not statistically significant. ($P>0.05$).

DISCUSSION

Somatostatin is a strong inhibitor of pancreatic secretion, and can relax Oddi's sphincter, stimulate the reticulo-endothelial system, and protect cells. Therefore it has been widely used in the treatment of acute pancreatitis and complications after pancreatic surgery. It is widely accepted that TCM has a therapeutic effect in promoting gastrointestinal peristalsis, protecting intestinal barrier function, depressing actions of cytokines and inflammatory media, improving pancreatic microcirculation, safeguarding pancreatic cells and subcellular organellae, and inhibiting the activation of pancreatin[6-8]. However, traditional Chinese medicines are not involved in the inhibition of external secretion by the pancreas. Administration of Chinese medicines is generally through the mouth or through a stomach tube. In the early stage of pancreatitis, these two routes can stimulate secretion by the pancreas, so aggravating auto-digestion of the pancreas and accelerating inflammatory exudates from it. In clinical practice it was also observed that patients with severe acute pancreatitis, especially those with enteroparalysis, underwent a repeated process of tube-feeding - gastrointestinal retention - gastrointestinal decompression - another tube-feeding, which could last for 24-48 h during the first 72 h. Therefore, in early treatment by TCM, in the first 72 h, the additional use of somatostatin could produce a synergistic action with traditional Chinese medicines and could also overcome, to some extent, the disadvantages of the administration route. A short-term use of somatostatin combined with traditional Chinese and Western medicine to treat severe acute pancreatitis could improve the treatment through a synergistic mechanism of the two therapies and decrease some adverse effects; besides, it would not be expensive. However, this innovative therapy remains to be further studied clinically.

There have been many researches on the assessment of severity and prognosis of severe acute pancreatitis. The APACHE II scoring system not only determines whether pancreatitis is mild or severe within the first 24 h of onset, but also assesses the severity of the patient's condition in the disease course. In addition, its sensitivity and specificity are relatively high[9]. In this study, the APACHE II scoring system was able to assess the condition of patients in the two groups both before and during treatment, and predict changes in their condition, thus providing evidence for further treatment. It was found that APACHE II scores on the seventh day after admission were lower in the somatostatin treatment group than in the basic treatment group, suggesting that the relief from severe acute pancreatitis may be attributed to comprehensive treatment with somatostatin.

C-reaction protein level is a single important index for early assessment and determination of the severity of severe acute pancreatitis[10]. This study found that the peak of serum C-reaction protein level occurred within 1-4 d of disease onset, and C-reaction protein level on the fourth and seventh days after treatment was significantly lower in the somatostatin treatment group than in the basic treatment group. This suggests that somatostatin may depress excessive inflammatory reactions. In terms of treatment opportunity, we suggest that somatostatin should be given immediately after admission and should be continued for 72 h, corresponding to the reaction period of C-reaction protein.

Findings from enhanced-CT scanning are the gold standard for diagnosing necrosis of the pancreas. They also accurately reflect local pathogenic changes in and around the pancreas. So, the diagnostic criteria derived from Balthazar-CT have been widely accepted and highly praised. Balthazar scores decreased after treatment in both groups, suggesting that there was an improvement of inflammation in and around the pancreas. Somatostatin accelerated the absorption of inflammation through its strong depression of pancreatic secretion. The fact that there was no significant difference between the two groups after treatment may be due to the short period of observation and incomplete absorption of the fluid around the pancreas.

In terms of morbidity of organ dysfunction and mortality rate, addition of somatostatin did not achieve a significant effect. There could be two reasons for this. (1) The dosage and duration of administration: somatostatin mainly inhibits the activation process of enzymes in the acinus in the early stage of pancreatitis; so it should be used as early as possible in order to achieve the best result. In the treatment of a pancreatitis animal model, administration of somatostatin before modeling was able to achieve good therapeutic effect. In this study, most of the patients were admitted after 48 h of onset. In addition, literature suggests the use of somatostatin for 5-7 d[11,12], and short-term use should be tested for effectiveness with larger sample sizes. (2) The sample size: the relatively small sample size of 60 cases may be a reason for different therapeutic effects. Meta analysis[13] has pointed out that the use of somatostatin in treatment of severe acute pancreatitis can significantly decrease the mortality rate, and that a single small sample size may lead to a false negative result.

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