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Effect of Xuesaitong on elderly patients with severe acute pancreatitis by selective arterial intervention therapy.

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Abstract

The aim of this study was to observe the effect of Xuesaitong on senile Severe Acute Pancreatitis (SAP) patients by selective artery interventional therapy. Sixty senile SAP patients were divided into a control group (32 cases) and an observation group (28 cases). In addition to Xuesaitong injection in the observation group, both the groups received the same local pancreatic artery infusion drugs. The curative effects of the two groups were compared. Blood amylase reduced in the observation group faster than in the control group (P<0.01). Compared with the control group, the results of the observation group were much better with regards to abdominal pain relief, recovery of bowel sound, radiographic improvement, reducing the complications and shorter hospital stays (P<0.05). The levels of serum TNF-α and IL-6 in the observation group decreased significantly than that in the control group (P<0.05). Selective arterial interventional therapy combined with Xuesaitong was more effective and helped to reduce complications, mortality, and length of hospital stay and improved the prognosis in elderly patients with SAP.

Keywords: Severe acute pancreatitis, Elderly/aged, Interventional therapy, Xuesaitong.

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Introduction

Fifteen to twenty five percent of cases of acute pancreatitis are clinically severe associated with complications, morbidity and mortality [1]. Occurrence of Severe Acute Pancreatitis (SAP) tends to increase in the elderly [2,3]. It has been reported that senile SAP patients (>60 years) accounted for about 45.7%, with mortality rate 16.2% [4]. At present, many advocate the use of early non-surgical treatment for SAP [5]. For elderly patients with SAP, because of their poor health and a possibility of greater risk of surgery, choosing the right treatment option, as soon as possible, is very important [6]. In recent years, with the development of sophisticated interventional techniques for SAP in our hospital and long-term clinical observation, it was found that the choice of traditional combined with western drug to administer in the interventional therapy can grasp the pathogenetic link of SAP from different aspects, give full play to its advantages of collaborative medication, and achieve good results in clinical practice. In the present study, 32 elderly patients with SAP admitted to our hospital from January 2004 to January 2013 were selected to perform selective arterial interventional injection treatment combined using Xuesaitong. The satisfactory results were reported in this paper.

Materials and Methods

Clinical data

Sixty elderly patients with SAP (aged>60 years) admitted from January 2004 to January 2013 were selected. Thirty two patients; 19 males and 13 females were included in the observation group (treated by adding Xuesetong) while 28 patients; 16 males and 12 females were included in the control group (without Xuesetong). All cases were diagnosed by clinical performance and CT examination, and were in line with the diagnosis and grading standards of acute pancreatitis developed by pancreatic disease study group. Gastroenterology of Chinese Medical Association in 2003: APACHE II scored eight points or more, Balthazar CT belonged to grade II or above excepting of bile duct obstruction combined SAP. The observation indicators of the two groups before treatment showed no significant difference (P>0.05), so they were comparable. This study was conducted in accordance with the declaration of Helsinki and with the approval from the Ethics Committee of the people's hospital of Xingtai. Written informed consents were obtained from all participants.

Treatment methods

Seldinger technique was used to perform selective catheterization *via* the right femoral artery to the celiac artery and iohexol angiography was done. After staining the blood vessels of the pancreas in the arterial and real phases, pancreatic

tissues were observed and positioned reference to CT and MR imaging. The lesions of pancreatic head were inserted into the duodenal artery, lesions of pancreatic tail were inserted into splenic artery, and diffuse lesions of whole pancreas were inserted into abdominal cavity. The catheter sheath and catheter were fixed at the puncture site after successful intubation with only partial tees being exposed. Then the patient was sent to the ward to connect with the micro-pump for infusion therapy, the infusion retention time was 7 days. Local arterial infusion drugs included; 0.1 mg octreotide once every 6 h, or the third generation cephalosporin quinolone antibiotics daily in sufficient quantities, while 400 mg Xuesetong injection solution (Kunming Pharmaceutical Co., Ltd. Xing Zhong, Zhunzi Z53021499, 20 mg) was pumped daily in the observation group. Conventional treatment, such as, early fasting and decompression, nutritional support, promoting gastrointestinal function, maintaining water, electrolyte and acid-base balance, pancreatic protection, or any impaired organ function and supportive treatment were the same for the two groups. In the course of hospital treatment, necrotic lesion clearance, drainage and fistula preparation were required by surgery due to exacerbations in the control or observation group, which was included in the cases suffering transit surgery.

Measurement indicators

Four milliliters of venous blood were collected from the subjects at the time of and after admission and treatment for 7 days. Serum specimens were stored at -70°C. Enzyme Linked Immunosorbent Assay (ELISA) was performed according to kit instructions (France Diaclone provide kit) to detect the levels of cancer necrosis factor-α (TNF-α) and Interleukin-6 (IL-6). The recovery time or improvement for patients' signs, symptoms during the hospitalization and the overall prognosis such as occurrence rate of complication, mortality, transit operation rate and average length of stay were observed and compared.

Statistical analysis

Each set of data was expressed as mean ± standard deviation ($\bar{x}$ ± s). SPSS13.0 software was used for analysis of variance. Correlated indicator detection of the symptoms from the time of admission to disappearance of signs of the two groups were analysed using t-test, comparisons of the rates were performed using check χ^2 test.

Results

Recovery time of clinical indicators and total hospitalization time

After treatment, performance results of the patients showed that the serum amylase recovery time of the observation group was significantly shorter compared with that in the control group (P<0.01), as well as the abdominal pain relieving time, bowel sounds recovery time, recovery time of WBC and CT examination improvement time were all shorter than that of the control group (P<0.05). The total length of hospital stay in the two groups had a significant difference (P<0.05), explaining the reason that the overall length of stay in the observation group may be reduced compared with that in the control group (Table 1).

Table 1. *Clinical indicator changes in the two groups of patients after treatment ($\bar{x}$ ± s).*

	Abdominal pain relief time (h)	Recovery time of bowel sound (d)	Recovery time of blood amylase (d)	White blood cell recovery time (d)	CT check improvement time (d)	Hospital stay (d)
Observation group	28.43 ± 6.7	5.1 ± 0.7	4.2 ± 1.4	7.8 ± 1.5	15.5 ± 2.5	25.9 ± 14.3
Control group	37.98 ± 8.4	6.2 ± 1.5	7.5 ± 1.9	8.8 ± 1.1	19.7 ± 1.8	33.6 ± 16.5
P value	<0.05	<0.05	<0.01	<0.05	<0.05	<0.05

TNF-α and IL-6 levels

Serum TNF-α and IL-6 levels of patients in the two groups showed no significant difference during admission (P>0.05) but decreased after 7 days treatment significantly in the observation group compared with the control group (P<0.05, Table 2).

Table 2. *TNF-α and IL-6 levels of the two groups before and after treatment ($\bar{x}$ ± s, ng/L).*

Group	TNF-α		IL-6	
	Before	7 d after treatment	Before	7 d after treatment
Observation group	43.6 ± 26.7	87.4 ± 17.8*	103.5 ± 26.5	72.64 ± 15.3*
Control group	138.5 ± 29.1	114.3 ± 26.7	109.7 ± 22.8	91.35 ± 18.4

Note: *vs.* before treatment, *P<0.01. *vs.* control group. P<0.05.

Complication rate, operation rate and mortality

In the comparison of the incidence of complications in the two groups, including pancreatic encephalopathy, Adult Respiratory Distress Syndrome (ARDS), Myocardial Infarction (MI), gastrointestinal bleeding, acute renal failure and pancreatic pseudocyst; 11/32 cases had complications in the observation group (34.37%) while 17/28 cases had complications in the control group (60.71%), both of which had significant differences (P<0.05). The transit operation rate and mortality had no significant difference (P>0.05, Table 3).

Table 3. *Morbidity and mortality rates in patients of the two groups (cases, %).*

Group	n	Complications	Transit surgery	Mortality
Observation group	32	11 (34.37)	4 (12.5)	3 (9.38)
Control group	28	17 (60.71)	6 (21.4)	4 (14.29)
P value		<0.05	>0.05	>0.05

Discussion

Severe Acute Pancreatitis (SAP) had features such as acute onset, more complications and high mortality (especially in elderly patients), even if they eventually survived, patients often had complications such as pancreatic dysfunction of the internal and external secretion [7,8]. The evidence-based guidelines of the United Kingdom recommend ICU treatment indications for the SAP of patients aged>75 years. Along with in-depth study of the physiological mechanisms of pancreatitis in recent years, pathology and pathogenesis of pancreatitis, multi-link nature and complexity of the pathological process had been accepted widely. Most scholars believed that in addition to trypsin digestion, the changes in inflammatory mediators, ischemia or reperfusion injury were caused by pancreatic microcirculation, the role of Oxygen Free Radicals (OFR), pancreatic barrier damage and other factors commonly led to the occurrence of SAP and the development of its complications [9-11].

Of all the above mentioned causes pancreatic microcirculation barrier and the following multiple organ damage doctrine caused by inflammatory mediators "waterfall effect" caught more and more attention [12,13]. Under normal circumstances, the pancreatic blood flow accounts for only 0.8% of the total circulation of the body. Thrombosis, inflammation of the pancreas and other factors easily led to local perfusion disorders and ischemic necrosis. SAP angiography showed that 58% of pancreatic artery had abnormalities such as cut branches, undeveloped and uneven thickness, suggesting that pancreatic perfusion disorder was a key factor to cause pancreatitis changes from the edema to necrosis, and was closely related with the evolution severity of the disease and complications [14]. Blood microcirculation can be regarded as the initiating factor of acute pancreatitis, which occurred throughout the entire SAP development process as an on-going mechanism of injury. Thus, when the SAP occurred, conventional systemic administration was ineffective to achieve effective concentration in the local pancreas, which was bound to affect the therapeutic effect. Because the pancreatic blood supply was mainly from the celiac artery, the intraperitoneal infusion therapy administered by artery could increase the plasma concentrations of pancreatic tissue, which had a greater advantage than intravenous administration. Recent studies showed that drug concentrations of pancreatic tissue by administration through selective arterial infusion reached 3 to 5 times of that of the intravenous route [15], which may greatly improve the effectiveness of drug therapy for SAP. Pancreatic regional arterial infusion therapy had advantages such as drugs directly flowing to the liver *via* the portal vein and small systemic drug toxicity side effects.

The Xuesaitong was refined from active ingredient (total saponins of *Panax notoginseng*) extracted from *Panax pseudoginseng* (Araliaceae). *Panax pseudoginseng* is a traditional Chinese medicine used in the relief of bleeding, swelling, pain and other functions [16]. More and more studies found that Xuesetong could dilate blood vessels to increase blood supply, then achieve the effectiveness of local pancreas blood supply by blocking calcium influx of vascular smooth muscle and reducing cytosolic calcium concentration of vascular smooth muscle. Breviscapine also had roles in lowering blood viscosity, preventing platelet aggregation, reducing platelet adhesion and so on, which can effectively improve pancreatic microcirculation, correct tissue ischemia and prevent necrosis, improve pancreatic tissue hypoxia tolerance thereby producing a protective effect on the pancreas. The study also showed that Xuesaitong could improve organizational superoxide dismutase and glutathione peroxidase activity, inhibit lipid peroxidation and reduce oxygen radical to damage the tissues. Xuesaitong can also significantly reduce the levels of serum TNF-α, IL-6 and other inflammatory mediators, which had a blocking effect in reducing their impact on the immune damage, the degree of pancreatic injury and the development of severe pancreatitis.

In this study, regional arterial infusion therapy was used for the treatment of older SAP, it was found that both the observation group and the control group could significantly alleviate the clinical signs and symptoms and rapidly improve their performance of biochemical indicators and imageology. By adding Xuesetong in the observation group, regional arterial infusion therapy had more pronounced effect compared with the control group (P<0.05). It has been confirmed that TNF-α and IL-6 were important inflammatory cytokines in the development of SAP, which not only played an important role in early period of acute pancreatitis, but also caused pancreatic necrosis and progression aggravated disease [17-20]. In our study, the levels of inflammatory cytokines before and after treatment were compared, it was found that Xuesetong could significantly reduce serum TNF-α and IL-6 levels of the observation group, the difference was statistically significant (P<0.05). In addition, compared with the control group, the effect of reducing incidence of complications and the shortening hospital stays of the observation group in elderly patients with SAP was more significant (P<0.05). Due to the limited sample size of this study, the comparisons of the

surgical intervention rate and overall mortality in the two groups had no significant differences (P>0.05), but eventually required surgery and total mortality of Xuesetong in the observation group were all lower than that of the control group. However, if the sample size was increased, it was observed that the required transit operation rate and mortality decreased significantly after adding Xuesetong in the regional arterial infusion therapy.

Through the above clinical observations, it was con-firmed that selective arterial interventional therapy associated with Xuesetong in elderly patients with SAP had significant efficacy, the possible mechanism of action was drugs playing roles in the artery infusion through the pancreas to increase the drug concentrations of pancreatic tissue. Xuesetong fully played the role of comprehensive advantages of the treatment of pancreatitis such as improving microcirculation, intracellular enhancing local effects of drugs, reducing blood viscosity, inhibiting cytokine release of inflammatory mediators and scavenging oxygen free radicals, in conjunction with octreotide, it could inhibit pancreatic secretion, the antibiotics can control the infection through the pancreatic blood obstruction barrier, thus more effectively controlling and reducing the systemic damage of Systemic Inflammatory Response Syndrome (SIRS) to various organs, reduce the complications and mortality of the senile SAP, also shorten hospitalization time and reduce the cost of treatment, which can be used in clinical practice. But artery interventional treatment was minimally invasive treatment with certain risk in the treatment of acute pancreatitis of elderly patients. The application needed certain conditions, technology and equipment, and the patient's vital signs must be closely monitored during treatment. Strengthening catheter care, observing the local availability of bleeding or hematoma puncture, the prevention of the intimal injury due to the arterial intubation and prolonged bed rest, which should be paid attention because of lower limb thrombosis formation.

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