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Clinical efficacy of ilaprazole combined with somatostatin on severe acute pancreatitis and the effects on oxidative stress and inflammatory response

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Abstract: This study investigates the clinical efficacy of ilaprazole combined with somatostatin on severe acute pancreatitis (SAP) and the effects on oxidative stress and inflammatory response. Seventy SAP patients were randomized to the control and observation groups, which received the somatostatin treatment and ilaprazole combined with somatostatin treatment for seven days, respectively. Results found that, the time of abdominal pain relief, time of serum amylase recovery, time of urinary amylase recovery and time of defecation recovery in the observation group were shorter than those in the control group ($P<0.05$). After the treatment, comparing to the control group, in the observation group the heart rate decreased ($P<0.05$), the mean arterial pressure and the central venous pressure increased ($P<0.05$), the serum levels of super oxide dismutase and glutathione peroxidase increased ($P<0.05$), and the serum levels of malondialdehyde, tumor necrosis factor α, interleukin-6, C-reactive protein decreased ($P<0.05$). In treatment of SAP, ilaprazole combined with somatostatin can enhance the curative efficacy, and decrease the oxidative stress and the inflammatory response in patients. In addition, it cannot increase the adverse reactions, with good safety.

Keywords: Ilaprazole, somatostatin, severe acute pancreatitis, oxidative stress, inflammatory response.

INTRODUCTION

Acute pancreatitis is defined as the inflammatory reaction of pancreatic tissue by autodigestion, edema, bleeding and necrosis due to a variety of causes. At present, the etiology of acute pancreatitis is not clear, which may be related to bile duct stones, bile duct obstruction, long-term drinking, vascular thrombosis, trauma, infection, hyperlipidemia, etc. (Majidi *et al*., 2017). Abdominal pain, nausea, vomiting, jaundice, dehydration and fever are the main symptoms of acute pancreatitis. The patients with mild acute pancreatitis may be self-healed, while severe acute pancreatitis (SAP) patients may suffer from secondary infections, peritonitis, shock or others, and even die. The vast majority of SAP patients have severe acute abdominal pain as the initial symptom. The abdominal pain is often located in the upper left abdomen or even the entire abdomen. Some patients have abdominal pain radiating towards the back. SAP seriously affects the health and life safety of patients (Mederos *et al*., 2021). At present, the clinical treatment of SAP is mainly to inhibit the activity of trypsin, promote the recovery of gastrointestinal function, and resist the infection (Waller *et al*., 2018). Among them, the use of somatostatin can strongly inhibit the synthesis and secretion of trypsin, thereby reducing the damage to pancreatic tissue by trypsin and improving the clinical symptoms of patients (Cao *et al*., 2021; Norouzi *et al*., 2023). However, in some patients the efficacy of single somatostatin use is not very good (Wang *et al*., 2016). Therefore, somatostatin should be used in combination with other drugs to improve the therapeutic effect. Ilaprazole is a proton pump inhibitor with strong inhibitory effect on gastric acid. It is an effective drug for clinical treatment of duodenal ulcer and various acidic diseases (Fan *et al*., 2019). In addition, ilaprazole can significantly attenuate indomethacin-induced small intestinal injury and maintain the integrity of the mucosal barrier (Li *et al*., 2022). Previous studies have found that the oxidative stress and inflammatory response are closely related to the acute pancreatitis (Singh *et al*., 2009; Pădureanu *et al*., 2022). This study investigated the clinical efficacy of ilaprazole combined with somatostatin on SAP and the effects on the oxidative stress and the inflammatory response.

MATERIALS AND METHODS

Patients

A retrospective analysis was made on 70 SAP patients in our hospital from August 2019 to August 2021. The patients were divided to the control group (35 patients) and observation group (35 patients). Control group contained 24 male patients and 11 female patients. The age was 18-85 years, with average 46.80±16.95 years. The disease course was 19.21±2.43h. Observation group contained 25 male patients and 10 female patients. The age was 20-79 years, with average 43.34±14.25 years. The course of disease was 18.33±3.16h. There existed no obvious difference in basic data among these two groups. This research obtained the approval of Tianyou Hospital Affiliated to Wuhan University of Science and Technology ethics committee.

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Inclusion criteria and exclusion criteria

Inclusive criteria: i) the pancreatitis was firstly diagnosed in patients; ii) the patients complied with the SAP diagnostic criteria; iii) the patients had good compliance. Exclusion criteria: i) the patients were pregnant or in lactating term; ii) the patients had malignant tumor; iii) the patients had severe cardiopulmonary basic diseases; iv) the patients had mental illness; v) the patients had used somatostatin or proton pump inhibitor within one week before going to hospital; vi) the patients were allergic to somatostatin or proton pump inhibitor.

Treatment methods

Both groups received routine treatment such as fluid resuscitation and nutritional support. On this basis, the patients in control group were treated by somatostatin (Hainan Zhonghe Pharmaceutical Co., Ltd., Haikou, China; 3mg drug dissolved in 48ml normal saline) through intravenous drip, with rate of 0.25mg/h, one per day, for 7 consecutive days. Based on treatment scheme in control group, the patients of the observation group received ilaprazole sodium (Lizhu Pharmaceutical Factory of Lizhu Group, Zhuhai, China; 10 mg drug dissolved with 100 ml normal saline) treatment through intravenous drip, with rate of 20 mg/h, one per day, for 7 consecutive days.

Recording of clinical symptom recovery time

During the treatment, the time of abdominal pain relief, time of serum amylase recovery, time of urinary amylase recovery and time of defecation recovery in two groups was recorded.

Measurement of hemodynamic indexes

Before and after treatment, the hemodynamic index heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP) in two groups were measured using the G30 ECG monitor (Philips Inc., Netherlands), respectively.

Dettection of serum oxidative stress and inflammatory response index

Before and after the treatment, peripheral venous blood was collected from the patients. Blood was centrifuged at 3000 rpm and 4^{o}C for 15 min for obtaining the serum. The coagulation function indexes (activated partial prothrombin time (APTT), prothrombin time (PT), fibrinogen) were determined using automated coagulation analyzer. The oxidative stress indexes (superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA)) and inflammatory response indexes (tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP)) were detected using Elisa according to the kit instructions.

Observation of adverse reactions

During treatment, the adverse reactions were observed. The incidence of adverse reactions was calculated.

STATISTICAL ANALYSIS

SPSS 22.0 statistical software was adopted to perform statistical analysis. Counting data (n or %) was compared by chi-square test. Measurement data (mean ±standard deviation) were compared using Student's t test. P value less than 0.05 indicated the statistically significant difference.

RESULTS

Clinical symptom recovery time

During the treatment, in the observation group the time of abdominal pain relief, time of serum amylase recovery, time of urinary amylase recovery, time of defecation recovery were shorter than they in the control group, respectively ($P<0.05$; table 1).

Hemodynamic indexes

Before treatment, there was no obvious difference in hemodynamic index such as HR, MAP or CVP between the two groups. After the treatment, comparing to before treatment, in two groups HR decreased ($P<0.05$), and MAP and CVP increased ($P<0.05$). Comparing to control group, in observation group HR was further decreased ($P <0.05$) and MAP and CVP were further increased ($P< 0.05$; table 2).

Oxidative stress indexes

Table 3 presented that the serum SOD, GSH-Px and MDA levels before treatment showed no obviously difference among two groups. After the treatment, in two groups SOD and GSH-Px levels were higher than those before treatment ($P<0.05$), and MDA level was lower than that before treatment ($P<0.05$). Comparing to control group, after treatment in observation group SOD and GSH-Px increased ($P<0.05$) and MDA decreased ($P< 0.05$).

Inflammatory response indexes

Before treatment the serum TNF-α, IL-6 and CRP levels presented no obvious difference among two groups. After the treatment, in each group each index decreased comparing to before treatment ($P<0.05$). In the observation group each index was lower than that in the control group ($P<0.05$; table 4).

Adverse reactions

During the treatment, only a small part of patients suffered from adverse reactions including diarrhea, dizziness/headache, chest tightness and nausea/vomiting. The incidence of adverse reactions presented no obvious difference among two groups (table 5).

DISCUSSION

Treatment focus of SAP is to reduce the secretion of digestive enzymes and improve the mucosal barrier function. Somatostatin is a protease inhibitor, which can effectively inhibit the release of glucagons, growth

Table 1: Clinical symptom recovery time in two groups.

Group	n	Abdominal pain relief	Serum amylase recovery	Urinary amylase recovery	Defecation recovery
Control	35	6.18±1.18	3.39±0.82	4.16±0.69	6.32±0.94
Observation	35	4.62±0.74	2.91±0.42	3.25±0.53	4.63±0.60
t		6.626	3.082	6.188	8.966
P		0.000	0.003	0.000	0.000

Table 2: Hemodynamic indexes in two groups.

	Group	n	Before treatment	After treatment	t	P
HR (beats/min)	Control	35	129.52±24.42	93.17±18.06	7.080	0.000
	Observation	35	132.34±20.38	81.63±16.6	11.413	0.000
	t		0.525	2.783		
	P		0.602	0.007		
MAP (mmHg)	Control	35	60.32±13.30	81.73±9.58	7.728	0.000
	Observation	35	62.19±15.24	88.30±11.72	8.035	0.000
	t		0.547	2.568		
	P		0.586	0.012		
CVP (cmH_2O)	Control	35	5.18±1.16	7.51±1.43	7.486	0.000
	Observation	35	5.42±1.32	8.72±1.66	9.205	0.000
	t		0.808	3.267		
	P		0.422	0.002		

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure.

Table 3: Oxidative stress indexes in two groups.

	Group	n	Before treatment	After treatment	t	P
SOD (U/L)	Control	35	46.80±7.06	58.16±13.30	4.463	0.000
	Observation	35	44.32±6.69	72.73±14.28	10.658	0.000
	t		1.508	4.417		
	P		0.136	0.000		
GSH-Px (μmol/L)	Control	35	32.20±5.94	46.42±5.06	10.781	0.000
	Observation	35	30.19±4.91	50.82±8.14	12.846	0.000
	t		1.544	2.716		
	P		0.127	0.008		
MDA (μmol/L)	Control	35	12.28±2.62	8.40±1.83	7.183	0.000
	Observation	35	13.36±1.95	5.62±1.28	19.631	0.000
	t		1.956	7.365		
	P		0.055	0.000		

SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde.

Table 4: Inflammatory response indexes in two groups.

	Group	n	Before treatment	After treatment	t	P
TNF-α (pg/ml)	Control	35	24.39±4.80	7.04±1.56	20.337	0.000
	Observation	35	25.33±5.13	6.21±1.25	21.434	0.000
	t		0.792	2.486		
	P		0.431	0.015		
IL-6 (pg/ml)	Control	35	31.07±5.06	18.17±3.37	12.553	0.000
	Observation	35	32.37±6.04	16.20±2.17	14.905	0.000
	t		0.976	2.908		
	P		0.332	0.005		
CRP (μg/ml)	Control	35	45.52±8.90	11.54±2.06	22.006	0.000
	Observation	35	42.18±7.31	10.06±1.65	25.390	0.000
	t		1.717	3.317		
	P		0.091	0.001		

TNF-α, tumor necrosis factor α; IL-6, interleukin-6; CRP, C-reactive protein.

Table 5: Adverse reactions in two groups.

Group	n	Erythra (n)	Dizziness/headache (n)	Chest tightness (n)	Nausea/vomiting (n)	Incidence (%)
Control	35	1	2	0	1	11.43
Observation	35	2	3	1	2	22.86
	χ^2					1.610
	P					0.205

Hormone, pepsin and gastrin, thus protecting the pancreatic cells and gastric mucosa (Klaff and Taborsky, 1987; Lloyd *et al*., 1997). In addition, it can inhibit the early inflammatory cascade reaction of SAP, and alleviate the symptoms of patients (Wang *et al*., 2018). In addition to the increase of pancreatic secretion, SAP patients are also accompanied by gastrointestinal motility disorder, which causes the increase of gastric acid secretion and aggravation of patient's condition (Gliem *et al*., 2021). Therefore, the treatment effect of somatostatin alone is limited and it needs to be combined with anti-acid drugs. Ilaprazole, as a proton pump inhibitor, can combine with H^+-K^+-ATPase to play an active role in acid inhibition (Shen *et al*., 2020). It can also improve the motility in the gastrointestinal tract and reduce the trypsin secretion (Kim *et al*., 2021). This study investigated the efficacy of ilaprazole combined with somatostatin on SAP. Results found that, in the observation group the time of abdominal pain relief, the time of serum amylase recovery, the time of urinary amylase recovery and the time of defecation recovery were shorter than the control group, respectively. This indicates that the efficacy of ilaprazole combined with somatostatin in treatment of SAP is better than single use of somatostatin. In addition, the hemodynamic monitoring is important to assess the condition of patients with SAP and the rescue outcome. In this study, after treatment, comparing to before treatment, in two groups HR was decreased and MAP and CVP were increased. Compared with control group, in observation group above indexes were further improved. This indicates that the combined treatment can further improve the hemodynamic level of SAP patients, which is associated with the synergistic effects of somatostatin and ilaprazole.

In the course of SAP, the tissue auto digestion can cause the oxidative/antioxidant imbalance, that is, the oxidative stress. In this condition, a large number of oxygen free radicals are produced. They can cause the lipid per oxidation damage of pancreatic tissue, finally leading to the irreversible necrosis of pancreatic tissues (Ma *et al*., 2021). SOD reflects the ability to eliminate the oxygen free radicals in the body. GSH-Px is the catalase of hydrogen peroxide decomposition, which can eliminate the oxygen free radicals, thereby inhibiting the lipid peroxidation. MDA can reflect the lipid peroxidation damage degree due to oxygen free radicals. These three indexes can evaluate the severity of oxidative stress in body (Zhu *et al*., 2020; Masomi-Bornwasser *et al*., 2021). In ous study, after treatment, in each group SOD and GSH-Px were higher than before treatment and MDA was lower than before treatment. After the treatment, comparing to control group, in observation group SOD and GSH-Px increased and MDA decreased. This suggests that the better efficacy of ilaprazole combined with somatostatin for SAP may be related to its enhanced effect in resisting oxidative stress.

Pathogenesis of pancreatitis is related to many inflammatory factor. TNF-α is an important factor causing damage to pancreas and extrapancreatic organs and tissues. When the body is in an inflammatory state, the level of TNF-α will rise sharply (Jiang *et al*., 2021). IL-6 has obvious proinflammatory effect, which can be used as a marker to reflect the inflammatory state of pancreatitis patients (Li *et al*., 2018). CRP is an important indicator to reflect the inflammatory state of pancreatitis patients, and its level can reflect the body damage degree from inflammatory reaction (Dix *et al*., 2022). In our study, after the treatment in each group serum TNF-α, IL-6 and CRP decreased comparing to before treatment. Each index in the observation group was lower than the control group. It is indicated that the combination of somatostatin with ilaprazole can exert the synergistic anti-inflammatory effect for SAP patients.

CONCLUSION

To sum up, in treatment of SAP, ilaprazole combined with somatostatin can enhance the curative efficacy, and decrease the oxidative stress and inflammatory response. In addition, it cannot increase the adverse reactions, with good safety. However, the number of enrolled cases is relatively small and long follow-up is not carried out. These are the limitation of this study. In the next study, the number of cases and observation time need to be increased, for further objectively evaluating clinical value of ilaprazole combined with somatostatin for treating SAP.

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