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Effect of Somatostatin Combined with Modified Dachengqi Decoction on Intestinal Function and Inflammatory Factors (TNF-α, IL-6, and IL-8) in Acute Pancreatitis

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HS and JS collected the samples.
HS analysed the data, conducted the experiments and analysed the results.
Both authors discussed the results and wrote the manuscript.

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SAP, Somatostatin, Dachengqi decoction, Intestinal function, Inflammatory factors

ABSTRACT

This article aimed to evaluate the effect of somatostatin combined with modified Dachengqi decoction on the improvement of intestinal function in patients with severe acute pancreatitis (SAP), and to explore its effect on the levels of inflammatory factors. Sixty patients with acute pancreatitis (AP) in the Department of Gastroenterology of Lin'an District First People's Hospital from February 2021 to February 2023 were grouped: controls and experimental group, 30 cases in each group. The controls received somatostatin and conventional treatment, and the experimental group adopted modified Dachengqi decoction based on the controls. After treatment, the incidence of complications in experimental group was lower as against controls ($P < 0.05$). The duration of gastrointestinal symptoms and recovery time of gastrointestinal function in experimental group were shorter as against controls ($P < 0.05$). The level of amylase (AMS) in blood and urine of two groups decreased ($P < 0.05$), more clearly in experimental group ($P < 0.05$). The levels of serum inflammatory factors in two groups decreased ($P < 0.05$), more clearly in experimental group ($P < 0.05$). The therapeutic effect of experimental group was better as against controls ($P < 0.05$). Somatostatin plus modified Dachengqi decoction can reduce the incidence of complications, shorten the clinical recovery time, and is conducive to improving the curative effect, which is worthy of promotion.

INTRODUCTION

Acute pancreatitis (AP) is a serious digestive disease with various clinical manifestations (Mas *et al*., 2022). Mild cases may only show abdominal pain, nausea, vomiting and other symptoms, while severe cases may show severe persistent abdominal pain, abdominal distension, increased intra-abdominal pressure, and other severe symptoms. Severe cases may also have complications such as pancreatic necrosis, abdominal infection, multiple organ dysfunction syndrome, and even endanger the life of patients (Guo *et al*., 2019). Clinically, AP is often divided into mild, moderate, and SAP according to the Revised Atlanta Classification (RAC) (Lee and Papachristou, 2019). The pathophysiological process of severe acute pancreatitis (SAP) is very complex. Several studies have shown that intestinal dysfunction is one of the common complications in SAP patients (Mederos *et al*., 2021; Szatmary *et al*., 2022).

Somatostatin is an endogenous polypeptide, which mainly treats SAP by inhibiting a variety of pancreatic endocrine hormones, reducing biliary pressure, and anti-inflammatory effects (Hall *et al*., 2023). The application of somatostatin has been verified to a certain extent in clinical practice (Guntur and Kholili, 2023), but the efficacy of somatostatin alone in SAP is still controversial. Studies have shown that somatostatin has a positive effect on the regulation of biliary pressure and the inhibition of inflammatory response, but it may have limitations in improving intestinal function and reducing the occurrence of complications (Hey-Hadavi *et al*., 2023). Therefore, there is an urgent need to seek new treatment strategies and drug combinations, which can help to improve the treatment effect of SAP, reduce the occurrence of complications, and further optimize the treatment strategy of pancreatitis.

Dachengqi decoction is a commonly used traditional

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Chinese medicine (TCM) formula. Some studies have shown that Dachengqi decoction can reduce pancreatic inflammatory response and pancreatic secretory function by regulating pancreatic secretion and biliary pressure (Oland and Hines, 2022). Therefore, combined application of somatostatin and Dachengqi decoction may have a synergistic effect, and the therapeutic effect on SAP may be more significant (Chen *et al*., 2022). Somatostatin reduces biliary pressure and pancreatic inflammatory response by inhibiting the release of endocrine hormones (Tang *et al*., 2022). Dachengqi decoction can regulate pancreatic secretory function and biliary pressure by clearing heat and detoxifying, promoting qi, and further reduce pancreatic inflammatory response (Chen *et al*., 2022). Therefore, the combined application of somatostatin and Dachengqi decoction can give full play to their respective advantages, and may be more effective in improving the symptoms of pancreatitis and reducing the occurrence of complications. This article aimed to investigate the effect of somatostatin combined with modified Dachengqi decoction on SAP patients and its effect on intestinal function and inflammatory factors. The incidence of complications (such as renal failure, abdominal compartment syndrome, peripancreatic abscess, and pancreatic pseudocyst), recovery time of symptoms and gastrointestinal function, blood and urine amylase (AMS) levels, and inflammatory factors were tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8 levels before and after treatment were compared between two groups.

MATERIALS AND METHODS

From February 2021 to February 2023, 60 patients with SAP admitted to the Department of Gastroenterology, Lin'an District First People's Hospital were enrolled and divided into the experimental group, who will receive somatostatin + Dachengqi decoction, and the controls who will be treated with somatostatin alone, 30 cases in each group. All patients met the diagnostic criteria of AP in the Chinese Guidelines for the Diagnosis and Treatment of AP (2021). The clinical data such as age, gender, onset time, etiology, and severity of the disease were collected and statistically compared between two groups.

AP was diagnosed by clinical symptoms, medical history, laboratory examination, ultrasound, or CT.

Pregnant and lactating women, patients with underlying diseases of the digestive system, hyperlipidemia, hypertension, hyperglycemia, diabetes, allergic constitution, and mental disorders, with serious organ diseases affecting drug metabolism, those who had been treated with glucocorticoid, immune, anti-inflammatory, anticoagulant, and other drugs in the past month, those in critical condition, physiological or pathological conditions and those who had received TCM treatment outside the hospital were excluded.

According to the Guidelines for the Diagnosis and Treatment of AP (2021 edition), the controls were given routine treatment of somatostatin (SL PHARM, Beijing, China, H20054016 (3mg) intravenously at a dose of 250 μg/h for 3 to 5 days.

The experimental group was treated with modified Dachengqi decoction (Rhubarb 15 g, *Magnolia officinalis* 27 g, immature orange fruit 15 g, mirabilite 9 g). If the abdominal pain symptoms were not obvious, and there were indicators of intestinal obstruction, hyperactive or weak bowel sounds, metallic sounds, and gurgling sounds. X-ray films showed pneumatosis and effusion in the small intestine, then the patients were administered 15 g of raw rhubarb, 10g of mirabilite, 10g of immature orange fruit, 10g of *Magnolia officinalis*, 10g of common aucklandia root, 10g of Chinese peony, 10g of golden thread. The decoction was decocted to 450 mL and infused through the gastric tube, 150 mL/time. If the effect was not good, the amount of medicine could be doubled, and bupleurum, radix alba, salvia miltiorrhiza, or safflower could be added at the same time. Combined with gastrointestinal decompression, rehydration, and anti-infection treatment, the patients were treated for 5 days.

For evaluation, 3 mL blood was drawn from the peripheral vein of the patients, before and after treatment, centrifuged at 3,000 r/min for 12 min, and the serum AMS level was detected by iodine-starch colorimetry. In addition, morning urine samples were collected, and the level of AMS in urine was determined by XC8001 automatic biochemical analyzer. The normal value of AMS in serum was 125 U/L, and the normal value of AMS in urine was 500 U/L.

The relief of symptoms and adverse reactions of the two groups were observed, and the relief time of abdominal pain, abdominal distension, nausea and vomiting of the patients was recorded.

SPSS23.0 statistical software was adopted to analyze the data. The enumeration data were expressed as n%, and χ^2 test was adopted.

RESULTS

All patients were clinically diagnosed with SAP. There was no obvious difference in gender, age, etiology, body mass index, and course of disease between two groups ($P > 0.05$) (Table I).

Table I. Effect of somatostatin combined with Dechen on general data of patients.

Group	Number of cases	Gender		Average age (years)	Cause			Body mass index (kg/m²)	Duration of illness (days)
		Male	Female		Full of food	Source of bile	Alcohol		
Controls	30	16	14	48.26±6.89	7	9	14	24.73±2.11	28-42
Experimental group	30	19	11	49.56±6.73	6	8	16	24.48±2.14	21-35
P	-	>0.05	>0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table II. Gastrointestinal symptoms and recovery time of gastrointestinal function ($\bar{x}$± sd).

Group	n	Abdominal pain	Abdominal distention	Nausea and vomiting	Recovery time of gastrointestinal function
Controls	30	11.28±1.39	13.63±1.28	12.39±1.21	15.72±1.90
Experimental group	30	6.63±1.07	7.29±1.16	7.65±1.02	8.34±1.73
P		< 0.05	< 0.05	< 0.05	< 0.05

Table III. Effect on somatostatin combined with *Dachengqi* on amylase (AMS) indices in blood and urine ($\bar{x}$± s, U/L).

Groups	n	Blood AMS		Urine AMS	
		Before treatment	Following treatment	Before treatment	Following treatment
Controls	30	1,473.22±95.62	296.56±27.32	3,143.89±336.97	933.62±50.09
Experimental group	30	1,488.79±93.74	141.89±22.39	3,217.45±341.03	876.98±51.28
P		> 0.05	< 0.05	> 0.05	< 0.05

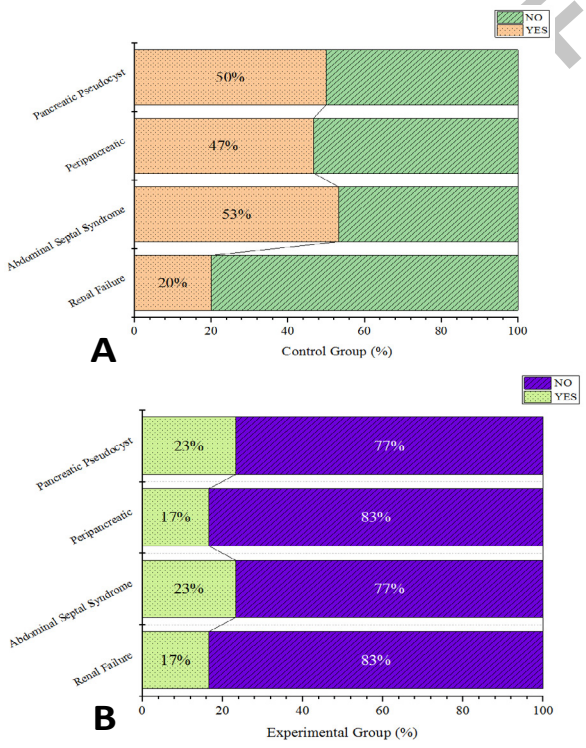

Fig. 1. Morbidity of each complication in the controls (A) and experimental group (B).

The results suggested that there was no obvious difference in the incidence of renal failure between two groups (P > 0.05). However, the incidence of abdominal compartment syndrome, peripancreatic abscess, and pancreatic pseudocyst was markedly lower in the experimental group than in the controls (P < 0.05) (Fig. 1).

The gastrointestinal symptoms of patients were relieved after treatment. The duration of abdominal pain, abdominal distension, nausea and vomiting and the recovery time of gastrointestinal function in the experimental group were shorter as against controls (P <0.05) (Table II).

Table III shows that the level of blood and urine AMS in the patients was lower as against before treatment, and the average value of blood and urine AMS in the experimental group was lower as against controls (P <0.05). As against the controls, the level of blood and urine AMS in the experimental group decreased more markedly post-treatment (P <0.05) (Table III). Moreover following treatment, the serum levels of TNF-α, IL-6, and IL-8 were markedly decreased in the two groups, although three was no statistically significant differences between two groups (Fig. 2).

The significant efficiency, effective rate, and total effective rate of experimental group were markedly higher as against controls (P < 0.05) (Fig. 3).

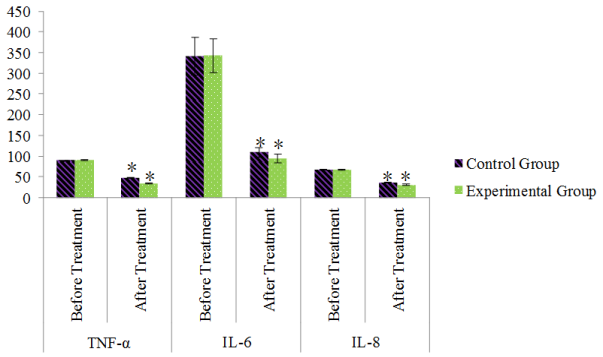

Fig. 2. Effect on somatostatin combined with Dachengqi on the levels of serum inflammation-related indexes in patients suffering from acute acute pancreatitis before and following treatment. Note: * As against controls, $P < 0.05$

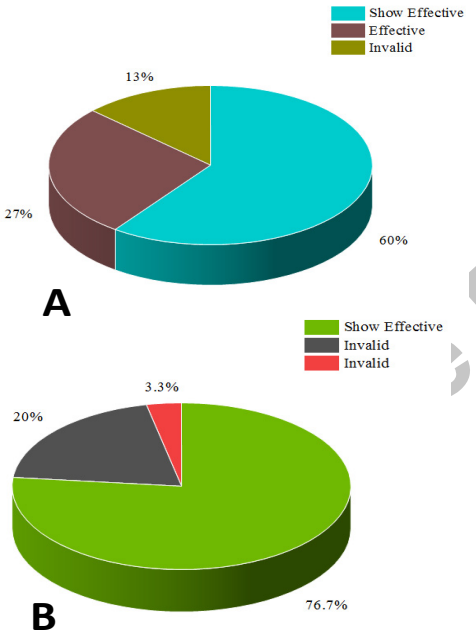

Fig. 3. Clinical treatment outcomes in the controls (A) and the experimental group (B).

Remarkable effect: Abdominal distension, abdominal pain, nausea, and other symptoms completely disappeared, and the AMS level in blood and urine returned to the normal range. **Effective**: Abdominal distension, abdominal pain, and nausea were relieved, and the level of AMS in hematuria was markedly decreased, but did not reach the normal value. **Ineffective**: There was no significant improvement in abdominal distension, abdominal pain, nausea, and other symptoms, and the levels of AMS and lipase in blood did not decrease or even increased.

The total effective rate was calculated as factor

Total effective rate = (marked effective + effective)/total number of cases × 100%

DISCUSSION

SAP is a severe pancreatic disease, and its pathogenesis is closely related to the self-digestion of the pancreas (Fang *et al*., 2023). The disease is usually caused by a variety of reasons, which makes the pancreas secrete too much trypsin, resulting in pancreatic enzymes digesting the pancreas's own tissues and organs (Connor, 2022). This condition can cause a series of clinical symptoms, including abdominal pain, abdominal distension, nausea and vomiting, and inflammatory response (Yu *et al*., 2022). Young men are more likely to suffer from SAP, which is characterized by rapid development, high risk, and high mortality (Al-Mamun *et al*., 2022). With the deterioration of the disease, it may also lead to complications such as peritoneal irritation sign, pancreatic necrosis, and abscess (Iannuzzi *et al*., 2022). AP is usually associated with overeating and/or biliary tract disease. Edema, hemorrhage, and even necrosis of the pancreas are the main features of AP. If accompanied by hemorrhage and necrosis, it is classified as hemorrhagic pancreatic necrosis, which belongs to a type of severe pancreatitis (de-Madaria *et al*., 2022). Some studies have shown that during the development of SAP, the release of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-8) is increased, while the production of anti-inflammatory cytokines (such as IL-10, TGF-β) is inhibited, resulting in the balance of pro-inflammatory and anti-inflammatory cytokines in the body being broken. The imbalance of these factors plays an important role in the pathogenesis of SAP (Wang-Liang *et al*., 2022). During the inflammation of SAP, many inflammatory factors released can activate immune cells and endothelial cells, and further release more inflammatory factors, forming a vicious cycle called a waterfall cascade, which will lead to systemic inflammatory response syndrome (SIRS). The occurrence of this reaction will have adverse effects on multiple organs such as cardiovascular, lung, kidney (Takada *et al*., 2022). In addition, with the increase of inflammatory factors, vascular dilatation, platelet aggregation, and coagulation dysfunction occur, leading to hemodynamic disorders. Vascular endothelial damage leads to increased vascular permeability, which further leads to plasma protein extravasation, tissue edema, and organ damage.

At present, western medicine combined with symptomatic treatment such as fasting, fluid resuscitation, nutritional support, and analgesia are usually used to alleviate the symptoms of early AP (Liu *et al*., 2023). Among them, somatostatin is one of the commonly used drugs. Somatostatin is a synthetic cyclic 14-amino acid peptide, which can reduce the activity of pancreatic enzymes and reduce the secretion of pancreatic enzymes by

the pancreas (Chen *et al*., 2022). In addition, somatostatin can also induce the expression of epidermal growth factor (EGF) in pancreatic tissue, promote the proliferation of pancreatic cells, and induce apoptosis of damaged pancreatic cells. Therefore, somatostatin can promote the repair of pancreatic cells (Michel *et al*., 2022). However, in the process of clinical treatment, the prognosis varies regardless of the efficacy of patients. On the one hand, the main reasons are individual differences in genetic background, underlying disease, age, severity of disease, physical condition, and so on. On the other hand, single medication results in single drug effect, which limits the application of somatostatin in individualized treatment (Horváth *et al*., 2022; Chao *et al*., 2023). Therefore, a single drug therapy may not be able to meet the needs of all patients, and further research and development of more individualized treatment strategies can better improve the prognosis and treatment effect of patients.

In order to improve the therapeutic effect, some studies have explored the possibility of using different drugs in combination or other treatment methods in recent years. For example, anti-inflammatory drugs, immunomodulators, and antioxidants used in combination with somatostatin may have a positive effect on the treatment of AP.

Dachengqi decoction is a commonly used TCM formula, which is mainly used to treat symptoms such as fever, abdominal pain, dysphoria, thirst. The composition of Dachengqi decoction includes Rhubarb, magnolia officinalis, immature orange fruit, mirabilite, common aucklandia root, Chinese peony, golden thread. Among them, rhubarb is the main medicine, which has the effect of clearing heat and clearing intestine (Wang *et al*., 2022; He *et al*., 2022). Pharmacological studies have shown that rhubarb has the functions of clearing heat and dispelling toxins, strengthening mucus-bicarbonate barrier, speeding up gastrointestinal digestion, preventing damage to digestive system organs, and reducing the occurrence of inflammatory reactions. Mirabilite can assist rhubarb to perform purgative action. Sulfate ions in mirabilite can indirectly reduce the absorption of water by the digestive system, accelerate the peristalsis of the digestive tract, and further play a role in clearing heat and dispelling toxins (Roychoudhury *et al*., 2022). Chinese peony has the effect of treating liver blood deficiency, nourishing Yin and nourishing blood, and relieving pain. The combination of magnolia officinalis, immature orange fruit can avoid qi and blood stasis and remove mites. Common aucklandia root incense has the functions of warming and tonifying the body, regulating qi and blood, relieving pain, and helping digestion (Rahman *et al*., 2022). In summary, Dachengqi decoction, as a TCM formula, can play a variety of pharmacological effects such as clearing heat, promoting qi, and activating blood circulation, protecting the pancreas and the mucus-bicarbonate barrier, and accelerating digestive tract peristalsis through the compatibility of its components. The combined effect of these pharmacological actions is the reason for the obvious clinical outcomes of Dachengqi decoction in the treatment of SAP. In recent years, due to the increased application of modified Dachengqi decoction combined with western medicine in clinical treatment, the curative effect and prognosis of patients have been markedly improved (Kang *et al*., 2022).

The results of this article show that somatostatin combined with modified Dachengqi decoction can markedly reduce the incidence of complications in patients with SAP, accelerate the recovery of symptoms and gastrointestinal function, reduce the level of AMS in blood and urine and inhibit the release of inflammatory factors. This may be caused by the combined effect of somatostatin with anti-inflammatory effect and Dachengqi decoction with anti-inflammation, removing dampness and blood stasis. However, this article also has some limitations, such as the relatively small sample size and single-center study design. Therefore, more large-scale, multi-center studies are needed to verify these results and further clarify the optimal application strategy of somatostatin plus modified Dachengqi decoction therapy in SAP.

Although the results of this article show a clear effect of somatostatin plus modified Dachengqi decoction therapy in SAP, further studies are needed to verify these findings and to explore the mechanism of action. Further large sample, multi-center randomized controlled trials should be carried out to better evaluate the safety and efficacy of this combination therapy and determine the best treatment regimen. For patients with different clinical types, the individualized application strategy of somatostatin combined with modified Dachengqi decoction can be further studied to improve the therapeutic effect and reduce the occurrence of adverse events. In addition, the study of the therapeutic mechanism is also necessary. The specific mechanism of its therapeutic outcomes can be further revealed by exploring the pharmacological properties, molecular pathways, and regulatory mechanisms of somatostatin and Dachengqi decoction on pancreatitis.

In conclusion, somatostatin plus modified Dachengqi decoction therapy, as a new treatment strategy, shows potential clinical application value in SAP. Future studies will further improve this treatment regimen and explore more combined treatment strategies in order to further improve the treatment effect of SAP, reduce the incidence of complications, and provide a more scientific basis for clinical practice.

CONCLUSION

These results indicate that somatostatin plus modified Dachengqi decoction has significant clinical efficacy and influence on SAP patients. Following treatment, as against controls, the incidence of complications was markedly lower, and the duration of gastrointestinal symptoms and recovery time of gastrointestinal function were shorter in the observation group. In the observation group, the level of AMS in blood and urine decreased more markedly, and the level of serum inflammatory factors also decreased more markedly as against controls. Clinical efficacy evaluation suggested that the therapeutic outcome of somatostatin plus Dachengqi decoction was better as against somatostatin alone.

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IRB approval

This study was carried out with the approval of Research Guidance Workshop Committee (Lin'an District First People's Hospital).

Ethical statement

All subjects agreed to sign an informed consent form with the consent of their family members. Approval for the conduct of the trial was obtained from the Hospital Ethics Society.

Statement of conflict of interest

The authors have declared no conflict of interest.

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