Int J Clin Exp Med 2020;13(8):6038-6043
www.ijcem.com /ISSN:1940-5901/IJCEM0111811

Original Article

The effect of *Rheum officinale* on recovery from severe pancreatitis by downregulating serum leptin, CRP, IL-10, and IL-6

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Received April 2, 2020; Accepted June 2, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Objective: This study aims to determine the changes in the serum leptin, C-reactive protein (CRP), IL-10, and IL-6 levels in pancreatitis patients after *Rheum officinale* treatment. Methods: 88 patients with severe pancreatitis were recruited. 44 patients receiving the conventional therapy were enrolled in the control group, while the remaining 44 patients taking *Rheum officinale* orally in additional to the conventional therapy were enrolled in the treatment group. The mortality rate, symptoms and signs after admission, and the changes in the time to the first defecation, the time to the disappearance of abdominal pain and tenderness, and the serum leptin, TNF-α, VEGF, CRP, IL-10, and IL-6 levels, were measured and recorded. Results: No significant differences were found regarding the time from onset to admission, the Acute Physiology and Chronic Health Evaluation II scores, the cause of the disease, or the incidence rate of acute respiratory distress syndrome between the treatment and control groups ($P>0.05$). The overall effective rate was 97.93% in the treatment group, which was significantly higher than it was in the control group (84.09%) ($P<0.05$). Meanwhile, the mortality rate and total hospitalization expense in the treatment group were significantly reduced, and the hospitalization duration, the time to the first defecation, and the time to the disappearance of abdominal pain and tenderness as well as the negative-conversion time of serum amylase were significantly shortened ($P<0.05$). Additionally, the leptin, TNF-α, VEGF, CRP, IL-10, and IL-6 levels were significantly reduced after the treatment ($P<0.05$). Conclusion: Rheum officinale can downregulate the serum leptin, CRP, IL-10, and IL-6 levels and promote the recovery of patients with severe pancreatitis.

Keywords: Severe pancreatitis, *Rheum officinale*, leptin, inflammatory factors

Introduction

In the clinic, severe pancreatitis is one of the common critical disease related to gastroenterology characterized by acute onset and complicated causes, and one that results in a particularly high mortality rate [1]. The most common cause of death is related to multiple organ dysfunction and systemic inflammatory response syndrome induced by acute pancreatitis [2]. The pathogenesis of acute pancreatitis remains elusive, although the traditional view believes that trypsin digestion in the pancreas, as well as an over-reaction of the inflammatory response and an abnormal activation of leukocytes, etc. play certain roles [3]. In addition to the inflammatory response, circulatory disturbances, excessive apoptosis, and bacterial translocation in the digestive tract (namely the "two-hit hypothesis"), are also thought to be common causes of the increasing mortality rate of severe pancreatitis [4].

There are a variety of factors associated with severe acute pancreatitis. For example, the blocked excretion of pancreatic fluid leads to inflammatory edema in the pancreas, and even ischemic necrosis, while necrotic pancreatic tissues produce and release a large number of inflammatory cytokines [5]. In the human body, there is a sort of polypeptide hormone (leptin), secreted and synthesized by adipocytes, with the main function of regulating the lipid metabolism. It is closely associated with the patient's

body weight and disease severity [6]. In recent years, *Rheum officinale* has been widely applied in the treatment of acute pancreatitis as it can effectively improve the symptoms and reduce the mortality [7]. However, whether *Rheum officinale* affects the expressions of inflammatory cytokines in pancreatitis is unclear. Our study aims to investigate the leptin, CRP, IL-10, and IL-6 levels in acute pancreatitis patients who received *Rheum officinale* treatment, which may provide guidance for acute pancreatitis treatment.

Patients and methods

Patients

88 patients treated in the Intensive Care Unit of Chongqing Fourth People's Hospital and diagnosed with severe pancreatitis from May 2016 to June 2017 were enrolled, including 48 males and 40 females aged 29-78 years (average age: 40.05±11.76). Inclusion criteria: Patients who were diagnosed with acute pancreatitis according to the guidelines of severe acute pancreatitis [7, 8]. Patients with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥8; patients with the onset of symptoms within 72 hours. Exclusion criteria: patients under age 18; patients who are pregnant; patients undergoing antibiotic treatment; patients with a malignancy; patients with other autoimmune diseases. Among the 88 patients, 44 received conventional therapy (the control group), while the remaining 44 patients were further treated with *Rheum officinale* orally in addition to the conventional therapy (the treatment group). Our study was approved by the ethics committee of Chongqing Fourth People's Hospital and all the patients signed an informed consent.

Treatment approaches

The patients received conventional therapy including electrocardiograph monitoring, fasting, gastrointestinal decompression, fluid infusion, correction of their water-electrolyte acid-base disturbances, relief from hyperacidity, inhibition of trypsin secretions, anti-infection treatment, and nutritional support. In the treatment group, the patients took an additional 50 g of *Rheum officinale* dissolved in 50 mL warm water via a stomach tube or through a nose-jejunum nutrition tube three times a day in addition to the conventional therapy.

Determination of the therapeutic effect

The therapeutic effect was evaluated as remarkably effective, effective, and ineffective according to the following criteria: Remarkably effective: All the clinical symptoms and clinical signs were significantly improved within 7 days after the treatment, and each blood index value returned to normal. Effective: All the clinical symptoms and signs were mildly relieved within 7 days after the treatment, and each blood index value showed a recovery trend. Ineffective: None of the clinical symptoms and signs showed any improvement or were further exacerbated within 7 days after the treatment, and each blood index value showed a deteriorating trend. The overall effective rate of treatment = remarkably effective + effective.

Measurement of the relevant parameters

20 mL fasting peripheral venous blood was drawn in the morning on the day before the treatment followed by an analysis of the blood biochemical parameters using a biochemical analyzer. The leptin level was determined using a radioimmunoassay, the TNF-α, CRP, IL-10, and IL-6 levels were measured using immunoturbidimetry, and the VEGF level was measured using ELISA.

Statistical analysis

SPSS 19.0 software was used for the statistical analysis. The measurement data were displayed as the mean ± standard deviation (SD) and assessed using unpaired Student's t-tests. The count data were presented as a percentage and assessed using chi-square tests. $P<0.05$ indicates a significance.

Results

Characteristics before treatment

No significant differences were observed in terms of age, gender, time from onset to admission, APACHE II scores, cause of the disease, or incidence rate of acute respiratory distress syndrome (ARDS) in the two groups ($P>0.05$) (**Table 1**).

Comparison of the curative effects after the treatment

After the treatment, the overall effective rate was 97.93% in the treatment group and this

Table 1. Comparisons of the general information in the treatment and control groups

General information	Treatment group (n=44)	Control group (n=44)	*P* value
Age (years old)	39.75±8.03	40.88±7.84	0.079
Gender (male/female)	23/21	25/19	0.053
Time from onset to admission (h)	19.55±15.21	20.87±10.87	0.121
APACHE II score (points)	15.23±4.72	15.09±3.29	0.536
Cause of disease			
Biliary pancreatitis	33	34	0.591
High-fat pancreatitis	6	8	0.098
Drug-induced pancreatitis	2	1	0.372
Autoimmune pancreatitis	1	0	0.405
Others	2	1	0.372
Incidence rate of ARDS (%)	25.29%	26.03%	0.083

Table 2. Comparison of the curative effects in the treatment group and the control group after the treatment

Group	n	Remarkably effective	Improved	Ineffective	Effective
Treatment group	44	33	10	1	43 (97.73%)
Control group	44	19	18	7	37 (84.09%)
P value					0.025

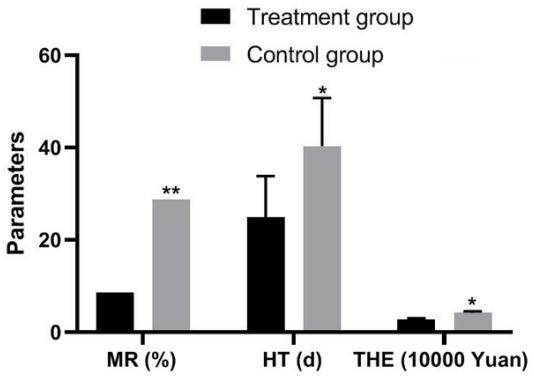

Figure 1. Comparisons of the mortality rate (MR), hospitalization times (HT), and total hospitalization expenses (THE) after the treatment. **P<0.01; *P<0.05.

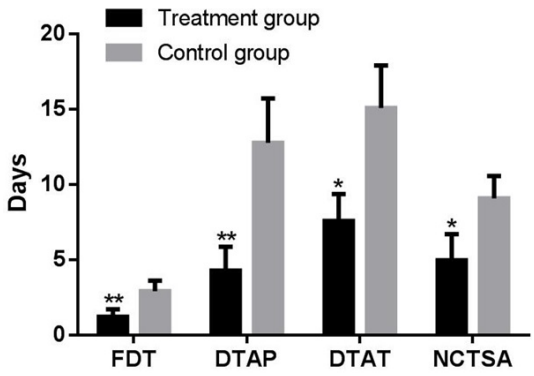

Figure 2. Comparisons of the symptom relief time, and the negative-conversion times of amylase after the treatment. **P<0.01; *P<0.05.

rate was significantly higher compared to the control group (84.09%) (P<0.05) (**Table 2**).

Comparisons of the mortality rate, hospitalization time, and hospitalization expense after treatment

After the treatment, the mortality rate and the total hospitalization expenses in the treatment group were significantly reduced, and the hospitalization duration was significantly shortened by the additional treatment of *Rheum officinale* compared to the conventional therapy (P<0.05) (**Figure 1**).

Comparison of the symptom relief time and the negative-conversion time after the treatment

After the Rheum officinale treatment, the time to the first defecation (FDT), the time to the disappearance time of the abdominal pain (DTAP) and tenderness (DTAT), as well as the negative-conversion time of serum amylase (NCTSA) were significantly decreased compared to the

Table 3. Comparisons of the leptin, TNF-α, and VEGF levels before and after the treatment

Group	n	Time	Leptin (μg/L)	TNF-α (ng/mL)	VEGF (pg/mL)
Treatment group	44	Before treatment	28.18±3.95	438.65±53.47	639±88
		After treatment	15.17±2.53*,#	67.79±30.59*,#	59±28*,#
P value (Before vs After treatment)			<0.0001	<0.0001	<0.0001
P value (Treatment vs control)			<0.0001	<0.0001	<0.0001
Control group	44	Before treatment	29.03±3.49	446.73±51.45	645±96
		After treatment	9.08±1.27*	208.33±27.59*	101±59*
P value (Before vs After treatment)			<0.0001	<0.0001	<0.0001

Note: Compared with before the treatment, *P<0.05. Compared with the control group after the treatment, #P<0.05.

Table 4. Comparison of the inflammatory factor levels before and after the treatment

Group	n	Time	CRP (mg/L)	IL-6 (Ug/L)	IL-10 (ng/mL)
Treatment group	44	Before treatment	15.95±2.3	0.88±0.10	3.39±0.76
		After treatment	5.9±2.0*,#	0.19±0.02*,#	0.83±0.29*,#
P value (Before vs After treatment)			<0.0001	<0.0001	<0.0001
P value (Treatment vs control)			<0.0001	<0.0001	<0.0001
Control group	44	Before treatment	16.08±2.1	0.90±0.13	3.32±0.95
		After treatment	10.03±1.8*	0.43±0.06*	1.79±0.34*
P value (Before vs After treatment)			<0.0001	<0.0001	<0.0001

Note: Compared with before the treatment, *P<0.05. Compared with the control group after the treatment, #P<0.05.

corresponding times in the control group (P< 0.05) (**Figure 2**).

Comparisons of the levels of leptin, TNF-α, and VEGF

Before the treatment, no differences were found in the serum leptin, TNF-α, and VEGF levels in the two groups (P>0.05). However, their levels were significantly downregulated after the treatment in both groups (P<0.05), and the levels were significantly lower in the treatment group than they were in the control group (P<0.05) (**Table 3**).

Comparisons of the inflammatory factor levels

Before the treatment, the serum CRP, IL-10, and IL-6 levels showed no differences between the two groups, but they significantly decreased after the treatment (P<0.05) with significantly lower levels in the treatment group (P<0.05) (**Table 4**).

Discussion

Severe acute pancreatitis has a complicated pathogenesis involving several factors [9]. In the past, the main treatment was surgery, but it was found that the incidence rates of complications and mortality rate remain high [10]. Recently, individual regimens based on general surgery combined with the patient's individual therapy have attracted extensive attention, such as conservative medical therapy and interventional therapy. However, there still is no specific therapeutic method or medicine for treating severe acute pancreatitis [11]. It was generally believed that patients with severe acute pancreatitis should receive oral or intravenous nutrition treatment, but long-term fasting often leads to gastrointestinal mucosal dysfunction and bacterial translocation. The induced systemic infection may aggravate the disease [12]. Therefore, the early recovery of enteral nutrition is recommended [13]. Patients often take somatostatin or its analogues to inhibit pancreatic juice secretions with a favorable curative effect in the clinic, but this strategy also impedes the recovery of gastrointestinal mucosal function while reducing the visceral blood flow [14]. Therefore, intestinal mucosal function is critical for the recovery of acute pancreatitis [15].

Rheum officinale is a kind of natural traditional Chinese medicine that can purge the cold. The treatment of acute pancreatitis with *Rheum*

officinale has a long history with several advantages, such as removing moist heat, detoxification, and promoting intestinal peristalsis [16]. In the treatment of acute pancreatitis, *Rheum officinale* can inhibit pancreatic enzyme activity, reduce inflammation, and protect the gastrointestinal mucosa [17]. Therefore, the oral administration of *Rheum officinale* can contribute to an effective improvement of the patient's condition, and a reduction in the pancreatic self-digestion and inflammatory factors. Consistent with these, in the present study, we found that *Rheum officinale* could effectively reduce the mortality rate, shorten the hospitalization time and decrease the total hospitalization expenses of acute pancreatitis patients. In addition, *Rheum officinale* can alleviate the symptoms and promote a decline in blood amylase.

In recent years, we've learned that several factors are involved in acute pancreatitis and the damage to systemic multiple organs. For example, TNF-α and IL-6 are mostly produced from activated monocytes and leukocytes infiltrating in the pancreatic tissues, which are involved in the regulation of the inflammatory response [18]. TNF-α can stimulate vascular endothelial cells to synthesize vascular endothelin and other substances, further leading to microcirculation disturbances and aggravating pancreatic tissue damage. Moreover, TNF-α can also prevent fibrinolysis, causing an over-activation of the coagulation system and the subsequent formation of thrombus in many capillaries in the body. It accelerates the spread of the inflammatory response in the body, and eventually causes systemic inflammation and organ dysfunction or even failure [19]. The plasma leptin level is correlated to the severity of the pancreatic dysfunction [20]. Consistent with the role of inflammation in acute pancreatitis, we found that the TNF-α, leptin, CRP, and IL-6 levels in patients with acute pancreatitis were significantly increased, but they were reduced after treatment with *Rheum officinale*, indicating that *Rheum officinale* can attenuate the inflammatory response of acute pancreatitis. However, a large cohort study should be performed to verify the findings.

Conclusion

In conclusion, *Rheum officinale* can effectively control the degree of inflammation, promote the recovery of gastrointestinal function, and improve the prognosis of patients with severe acute pancreatitis.

Disclosure of conflict of interest

None.

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