

Clinical study on the treatment of acute pancreatitis with external application of Yi-Dan Therapy based on the method of “stagnation requiring dispersion”: study protocol for a randomized controlled trial

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Author contributions

Pei-Xin Ge wrote the original draft. Bo-Yi Jia was mainly responsible for supervision, review and editing. Nai-Wei Zhang and Xiao-Na Zhang validated the draft. Li-Bao An conducted formal analysis. Qiao-Yan Zhang and Yan-Mei Cai were responsible for data curation and methodology. Shao-Dong Hao conducted literature search. Hong-Jie Cheng was in charge of the project and provided the article idea.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

AP, acute pancreatitis; TCM, traditional Chinese medicine; RCT, randomized clinical trial; AMY, serum amylase; CT, computed tomography; CRP, C-reactive protein; WBC, white blood cell; VAS, visual analog scale; PCT, procalcitonin; APACHE-II, acute physiology and chronic health evaluation II.

Citation

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Abstract

Background: Acute pancreatitis is an unpredictable and potentially lethal disease, causing tremendous pain in patients. The initial treatment of acute pancreatitis in modern medicine is supportive, but it is generally ineffective in relieving abdominal pain and distension. Traditional Chinese medicine has been shown to be more effective in regulating the body's homeostasis and reducing the clinical symptoms of pancreatitis. Yi-Dan ointment, derived from Dahuang-Mudan Decoction, is an effective external ointment for treating acute pancreatitis. The aim of this trial is to investigate the clinical efficacy of Yi-Dan ointment, providing a valuable complement to existing treatment options for pancreatitis. **Methods:** This is a randomized controlled clinical trial with two parallel groups. Patients in the control group were given basic treatment and nursing for 7 days; in the treatment group, Yi-Dan ointment was applied externally in addition to basic treatment and nursing. The main indicator is the overall efficacy, serum amylase, acute physiology and chronic health evaluation II score, symptom score, inflammatory markers, and classification of computed tomography. **Conclusion:** The trial results will provide high-quality evidence for Yi-Dan ointment, and provide a complement to existing treatment options for pancreatitis.

Keywords: acute pancreatitis; traditional Chinese medicine; external treatment; Yi-Dan ointment; randomized controlled trial

Background

Acute pancreatitis (AP) is an unpredictable and potentially lethal disease. It is also the most prevalent gastrointestinal disease necessitating urgent hospital admission. The incidence of AP has exhibited an annual increase of 3.07% overall, contributing to an augmented burden on health healthcare systems [1].

While the treatment strategies for acute pancreatitis have evolved, optimal management remains an area of concern [2]. The initial treatment of acute pancreatitis in modern medicine is supportive, including vigilant monitoring of vital signs, fluid balance, pain management, and nutrition. Specific measures encompass fasting, anti-inflammatory, inhibition of pancreatic enzyme secretion, and pancreatic enzyme activity. This treatment has a definite anti-inflammatory effect, but it is generally ineffective in relieving abdominal pain and distension. Patients still feel great pain, and the long-term efficacy needs to be improved.

Traditional Chinese medicine (TCM) has exhibited greater success in restoring systemic homeostasis and ameliorating clinical symptoms associated with pancreatitis, whereas the majority of modern medicines merely give local alleviation [3].

Yi-Dan ointment (produced by Fangshan Hospital of Beijing University of Chinese Medicine) is an external ointment designed for the treatment of AP. It contains six Chinese herbs: *Rhei Radix et Rhizoma* (Sheng Da Huang in Chinese), *Natrii Sulfas* (Mang Xiao in Chinese), *Persicae Semen* (Tao Ren in Chinese), *Moutan Radicis Cortex* (Dan Pi in Chinese), *Benincasae Semen* (Dong Gua Ren in Chinese), and *Borneolum Syntheticum* (Bing Pian in Chinese).

In clinical treatment, we found that it can shorten the time to first bowel movement, alleviate pain, and lower C-reactive protein (CRP) levels in patients with AP. This trial aims to investigate the clinical efficacy of Yi-Dan ointment in the treatment of AP through a randomized controlled clinical trial, thus providing a valuable complement to existing treatment options for pancreatitis.

Methods

Design and registration

This is a randomized clinical trial (RCT), with two parallel groups and a 1:1 allocation ratio, scheduled to run from June 2020 to May 2024. Protocol follows the SPIRIT 2013 checklist, and the flowchart of the study design is illustrated in Figure 1. The schedule is shown in Table 1. Approval for this study was obtained from the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine (Approved Number of ethic committee: FZYLK-2020-005). The trial protocol was registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR2000034545). In case of any necessary protocol modifications, notifications will be duly submitted to the Beijing Municipal Health Commission and the Ethics Committee of Fangshan Hospital, Beijing University of Chinese Medicine.

Participant recruitment strategy

Patients will be recruited through four hospitals: Fangshan Hospital of Beijing University of Chinese Medicine, Beijing Hepingli Hospital, Liangxiang Hospital of Fangshan District, Beijing, and the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine. Treating physicians will provide participants with detailed explanations. And informed consent forms will be signed.

Inclusion criteria and exclusion criteria

Diagnostic criteria. The diagnostic criteria for AP are based on the criteria of the Guideline for the diagnosis and treatment of acute pancreatitis in China (2019 Shenyang) [4]. The diagnosis hinges on the fulfillment of two out of three criteria:

- (1) Manifestation of symptoms of abdominal pain consistent with AP (acute, sudden, persistent, severe upper abdominal pain, often radiating to the back);
- (2) Serum amylase (AMY) and/or lipase levels ≥ 3 times the upper limit of the normal range;
- (3) Imaging findings such as abdominal ultrasound or computed tomography (CT) or magnetic resonance imaging demonstrating characteristic changes associated with AP (pancreatic edema or peripancreatic effusion).

AP patients are categorized based on the following criteria:

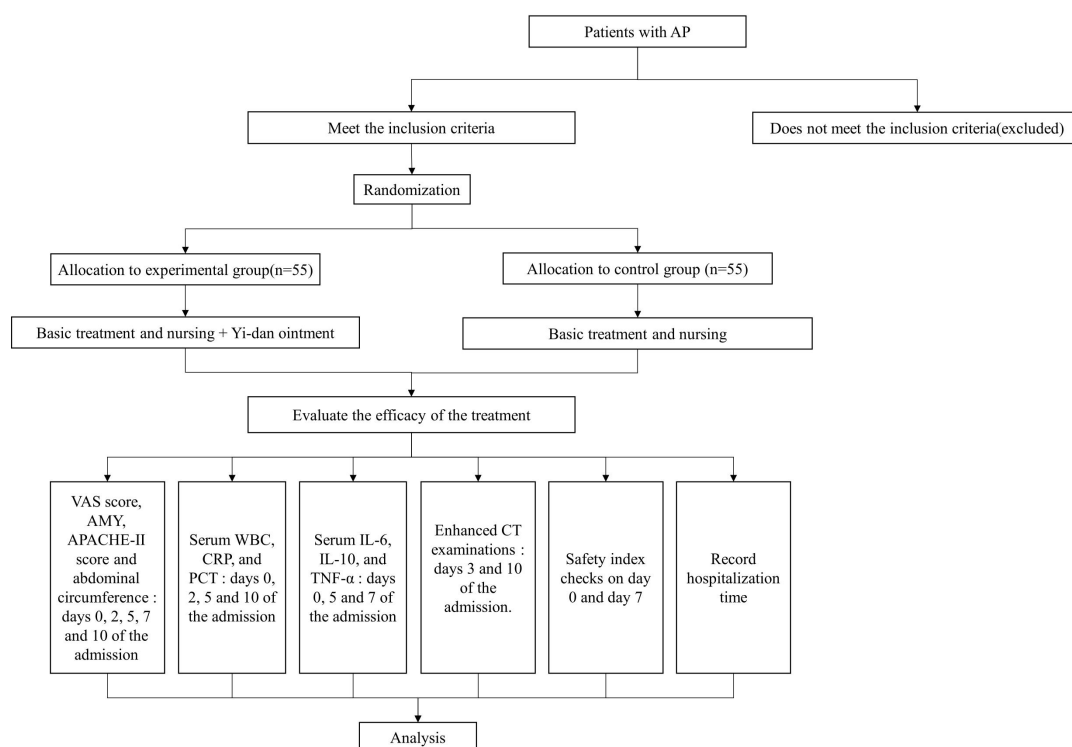
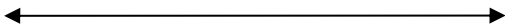
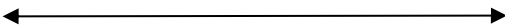


Figure 1. Flowchart of the study design. AP, acute pancreatitis; AMY, serum amylase; VAS, visual analog scale; CT, computed tomography; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; APACHE-II, acute physiology and chronic health evaluation II.

Table 1 Schedule of enrolment, interventions, and assessments

	Study Period										
	Allocation						Post-allocation				
Time point	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Enrollment											
Informed consent form	√										
Physical safety examination and vital signs	√										
Randomization	√										
Intervention											
Basic treatment and nursing for the control group											
Basic treatment and nursing + Yi-Dan ointment for the treatment group											
Assessment											
VAS score	√		√			√		√			√
APACHE-II score	√		√			√		√			√
Abdominal circumference	√		√			√		√			√
Serum AMY	√		√			√		√			√
Serum WBC	√		√			√					√
Serum CRP	√		√			√					√
Serum PCT	√		√			√					√
Serum IL-6	√					√		√			
Serum IL-10	√					√		√			
Serum TNF-α	√					√		√			
Enhanced CT				√							√

VAS, visual analog scale; APACHE-II, acute physiology and chronic health evaluation II; AMY, serum amylase; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; CT, computed tomography.

Mild acute pancreatitis: clinical manifestations and biochemical changes of AP without organ failure or local or systemic complications.

Moderately severe acute pancreatitis: clinical features and biochemical changes of AP, with transient organ failure (lasting < 48 h), or with local or systemic complications.

Severe acute pancreatitis: clinical features and biochemical changes of AP, and persistent organ failure (lasting > 48 h).

Inclusion criteria. (1) Aged 18–75 years.

(2) Meet the diagnostic criteria of AP.

(3) Sign informed consent.

Exclusion criteria. (1) Patients with severe primary diseases such as cardiovascular, cerebrovascular, liver, kidney, and hematopoietic systems.

(2) Patients with mental disorders that hinder their ability to cooperate.

(3) Patients concurrently participating in clinical trials of other drugs at the same time or are using drugs with similar therapeutic effects as the experimental drugs.

(4) Patients with skin damage or skin diseases in the abdomen.

(5) Pregnant or lactating women.

(6) Patients with known allergies to Chinese herbal medicine.

Sample size calculation

This project summarizes the treatment experience from long-term clinical practice and calculates the 20% shedding rate based on the results of previous studies. As a result, each group will consist of 55 cases, for a total of 110 cases across both groups.

Randomization

Patients will be randomized using random numbers, which will be stored in opaque envelopes. Random numbers will be generated using Excel, with the odd number assigned to the treatment group and the even number assigned to the control group. Envelopes will be opened upon patient enrollment. The allocation ratio of cases in the two

groups was 1:1.

Blinding

The study was a randomized controlled single-blind pilot study, with blinding applied to data processors.

Intervention

Patients in the control group were given basic treatment and nursing; in the treatment group, Yi-Dan ointment was applied externally in addition to basic treatment and nursing.

Basic treatment and nursing refer to the 2013 Chinese Clinical Practice Guidelines for Acute Pancreatitis in Emergencies and the Consensus on acute pancreatitis management of combination of Traditional Chinese Medicine With Western Medicine 2017 Standard [5, 6]: general nursing; no food or drink; oxygen inhalation therapy; close monitoring of vital signs; gastrointestinal decompression if necessary; fluid resuscitation; correction of disorders of glucose metabolism and water-electrolyte disturbance; antibiotic anti-infection treatment for biliary pancreatitis or concurrent extra-pancreatic infection; parenteral somatostatin 6 mg/24 h continuous pumping for 72–120 h to reduce endocrine and exocrine secretion of the pancreas; intravenous drip ulinastatin 100–200 thousand IU, 3 times/day to inhibit the activity of trypsin, phospholipase, plasmin, and elastase; intravenous drip pantoprazole sodium 80 mg, 1 time/day, to inhibit gastric acid secretion; enema, analgesic and sedative treatment as appropriate.

In the treatment group, alongside the above-mentioned standard treatment, external application of Yi-Dan ointment is added: take the Yi-Dan ointment 180 g each time and apply to the upper abdomen and the left upper abdomen, following the division of the nine abdominopelvic regions, 7:00–9:00 and 19:00–21:00 every day for a duration of 7 days. The composition of Yi-Dan ointment and the ointment preparation process are as follows: *Rhei Radix et Rhizoma* 50 g, *Natrii Sulfas* 50 g, *Persica Semen* 30 g, *Moutan Radicis Cortex* 30 g, *Benincasae Semen* 10 g, *Borneolum Syntheticum* 10 g.

The above herbs are ground into 200 mesh powder by a special apparatus and mixed into a thick paste with an appropriate amount of yellow wine

Data collection

Primary indicator. The primary indicator in this study is the overall, assessed in terms of symptom, AMY, and acute physiology and chronic health evaluation II (APACHE-II) score. The overall efficacy is determined by referring to the *Expert consensus on TCM diagnosis and treatment of acute pancreatitis (2017)* [7]. It is categorized into four levels: cured, markedly effective, effective, and ineffective, and the overall efficacy is calculated by the total number of cured, markedly effective, and effective cases.

Cured: symptoms and signs disappear within 5 days for mild cases, with all laboratory indicators returning normal; or the above criteria are met within 10 days for severe cases.

Markedly effective: symptoms and signs completely resolve within 5 days for mild cases, along with significant improvement in laboratory parameters; or in severe cases, the above criteria are met within 10 days, but comorbidities do not disappear completely, or APACHE-II are reduced by more than 50%.

Effective: improvement in symptoms and signs and improvement in laboratory parameters within 5 days for mild cases; or improvement in clinical symptoms and signs within 10 days for severe cases, recovery of relevant ancillary tests and imaging (including CT) compared to admission, but not to normal, or reduction of APACHE-II score by less than 50%.

Ineffective: no change or worsening of clinical symptoms and signs within 5 days for mild cases; or no change in clinical symptoms and signs within 10 days for severe cases, or aggravation and transfer to surgery, or reduction of APACHE-II score by less than 30%.

Secondary indicators. Secondary efficacy indicators encompass symptom scores, inflammatory markers, and CT classification. Symptom score scale was developed through extensive discussions by the research team referring to the *Consensus opinion on the diagnosis and treatment of acute pancreatitis with Chinese and Western medicine, 2017* [6]. This scale comprises primary symptoms and secondary symptoms. The inflammation indicators include serum white blood cell (WBC), CRP, procalcitonin (PCT), IL-6, IL-10, and TNF- α .

Primary symptoms: abdominal pain and distension. To assess the level of pain, the visual analog scale (VAS) is employed, with a 100 mm vertical scale. The 0 scale was specified as the minimum, namely, no pain or abdominal distension, and the 100 mm scale was specified as the maximum and unbearable pain or abdominal distension. Patients were asked to make a mark at the point where they thought it could reflect the level of pain and abdominal distension, and the reading at the mark was used as a score using the VAS scale method. Abdominal circumference was used to assess the patient's abdominal distension. Take the belly button level and measure the abdominal circumference with a soft ruler, which should be completely close to the body but not tighten the abdomen, and record the abdominal circumference value

Secondary symptoms: nausea and vomiting; depression and irritability, frequent sighing; belching; hiccup; yellow skin and eye; weakness and poor appetite; alternate attacks of chill and fever; dysphoria; fever aggravated at night; abdominal masses; unconsciousness; skin spots; difficulty and pain in micturition with dark-colored urine; anuria and constipation.

All symptoms are categorized into 4 levels: none, mild, moderate, and severe, with 0, 2, 4, and 6 points for the primary symptoms and 0, 1, 2, and 3 points for the secondary symptoms.

Observation time points. Various assessments will be conducted at specific intervals during the patient's admission to evaluate symptoms and health indicators:

VAS score, AMY, APACHE-II score, and abdominal circumference will be measured on days 0, 2, 5, 7, and 10 of the patient's admission to evaluate the severity of the symptoms such as abdominal pain and distension.

Serum WBC, CRP, and PCT will be collected on days 0, 2, 5, and 10

of the patient's post-admission to evaluate the inflammatory markers.

Serum IL-6, IL-10, and TNF- α will be collected on days 0, 5, and 7 of the patient's post-admission to evaluate the patient's inflammatory markers and other conditions.

Enhanced CT examinations will be taken on days 3 and 10 post-admission.

The timing of the first bowel movement and evacuation will be recorded.

To ensure the precision and consistency of the results, all team members will receive training throughout the program so that all understand the process of program implementation. The VAS score and abdominal circumference measurements will be conducted by three senior mid-level or higher with the necessary technical qualifications in the team. The collection of relevant signs and symptoms is carried out by two senior attending doctors or physicians or those with higher technical titles. In the case of a discrepancy between the two assessments, the judgment of the senior physician with the higher technical title will take precedence.

Safety indicators. Real-time monitoring of patients' vital signs, liver and kidney function, electrocardiogram, and other relevant indicators. In the event of an adverse reaction such as allergies, treatment will be promptly halted, and appropriate actions will be taken, with detailed records kept.

Discontinuation and withdrawal

- (1) Patient's condition worsens and requires additional treatment.
- (2) Patient requests for withdrawal.
- (3) Patients with allergic reactions.

Data management

Data management for this study involves a dedicated team member responsible for data entry and collation. A second team member checks the data, and the project quality controller conducts data sampling. Data is collated and improved quarterly during the project's implementation, with mid-term and year-end summaries carried out annually. Quality control meetings are held to review and propose solutions to any issues that arise during the study. The results will be published in the form of a paper in a publicly accessible academic journal.

Quality control measures

To carry out quality control supervision throughout the process, a quality control team will be established, with a designated quality control officer appointed by the study leader.

To ensure the standardization and consistency of the external application of pancreatic explants, uniform training is provided to members of the subject group.

To ensure the safety and reliability of the medicinal materials and the consistency of the medicinal effects, the pharmacy department of Fangshan Hospital of Beijing University of Chinese Medicine is responsible for the preparation of Yi-Dan ointment.

To avoid subjective influence, the team members responsible for statistical analysis will not participate in other processes.

Confidentiality

This trial will adhere to all applicable data protection laws in full compliance. All essential and suitable measures will be taken to protect patient's privacy and personal information in perpetuity. Blood samples will be destroyed after use.

Statistical analysis

Statistical analysis will be conducted using SPSS 21.0 software. All data measures will be expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and if the measures meet the normal distribution, one-way ANOVA will be applied when comparing between multiple groups, q-test will be used when comparing between groups, and factorial design ANOVA will be used to analyze the synergistic effect of the analyses. For data with non-normal distribution, the rank sum test will be used. Counting data will be analyzed using the chi-square test.

Linear correlation analysis was used for correlation. The significance level for all tests will be set at $P < 0.05$.

Discussion

AP is a condition characterized by the sudden activation of pancreatic enzymes, which has a digestive effect on the pancreas and surrounding organs, and is characterized by a local inflammatory response in the pancreas, even leading to organ dysfunction. Severe abdominal pain is the most predominant and distressing symptom for patients. According to WHO's pain treatment ladder, AP patients require adequate pain medication. However, there is currently no specific analgesic that is consistently safe and effective. Treatment typically follows the WHO's analgesic protocol [2, 8]. Additionally, there is a need for pharmacological interventions or strategies that can mitigate the early response of the systemic inflammatory response syndrome [2].

TCM offers a complementary and alternative approach to managing AP [9]. It is proven to be highly effective in restoring the intestinal barrier and intestinal motor function, preventing activation of inflammatory pathways, enhancing antioxidant and anti-inflammatory effects, inducing apoptosis of acinar cells, strengthening immunity, and mitigating calcium overload [10, 11]. TCM can play a vital role means of preventing and halting the progression of AP.

In TCM theory, the fundamental pathogenesis of AP is an obstruction of Qi in the fu-viscera (which means the Qi cannot circulate smoothly in the fu-viscera of the body). Treatment principles include purgation, catharsis, activation of blood circulation, and resolution of stasis. Currently, the TCM treatment method encompasses internal and external approaches. The latter has unique advantages in the treatment of AP in particular. As an external treatment method, external application is characterized by its effectiveness and rapid onset of action. It directly targets the abdominal area through the skin, providing relief without adding stress to the patient's gastrointestinal tract. So the external application method is simple, painless, easily accepted, and widely applicable in clinical practice [12].

Feasibility of Yi-Dan ointment for the treatment of AP

The Yi-Dan ointment is rooted in the theory of *Huang Di Nei Jing* that "stagnation requiring dispersion", and is derived from Dahuang-Mudan Decoction in *Synopsis of Golden Chamber (Jingui Yaolüe)*. Clinical trials have confirmed that Dahuang-Mudan Decoction enema can treat AP by inhibiting the inflammatory response, regulating pancreatic microcirculation, countering oxidative damage, and scavenging free radicals [13, 14]. Animal experiments have demonstrated that oral administration of the decoction can mitigate pancreatic injury, colon inflammation, and lung pathological damage. The mechanism of action may be related to the inhibition of signaling pathways, such as the HMGB1/RAGE/NF- κ B signaling pathway, TLR4/MYD88 signaling pathway, and PI3K/AKT signaling pathway [15–17]. In TCM theory, *Rhei Radix et Rhizoma* can eliminate stasis, purge fire, and relax bowels. *Moutan Radicis Cortex* can clear heat and promote blood circulation. *Natrii Sulfas* can soften and resolve mass. *Persicae Semen* can promote blood circulation and resolve stasis. *Benincasae Semen* can expel pus and eliminate carbuncles. *Borneolum Syntheticum* can clear heat and resolve mass. In summary, the Yi-Dan ointment has the effects of relieving congestion and dispersing stagnation, harmonizing the flow of vital energy for relieving pain, and promoting blood circulation for removing blood stasis, which aligns with the principles of AP treatment. Research shows that *Natrii Sulfas* possesses anti-inflammatory, diuretic, and detumescent qualities. The external application can help absorb abdominal moisture and reduce abdominal distension and intestinal swelling [9]. *Rhei Radix et Rhizoma*, which is frequently used as an adjuvant treatment in China's AP therapy guidelines, has shown positive clinical effects [6, 7, 18, 19]. External application of *Rhei Radix et Rhizoma* and *Natrii Sulfas* can promote intestinal peristalsis,

lower intra-abdominal pressure, enhance microcirculation, and reduce inflammatory reaction [20]. *Persicae Semen* can protect the intestinal barrier, reduce bacterial translocation, stabilize pancreatic vascular function, and enhance pancreatic microcirculation [21, 22]. *Moutan Radicis Cortex* has antibacterial and anti-inflammatory effects. One of its main components, paeonol, protects the pancreas [23]. *Borneolum Syntheticum* not only has antibacterial, anti-inflammatory, and analgesic effects but also increases the intercellular space and promotes the transdermal absorption of drugs [24]. Therefore, the biological mechanisms of Yi-Dan ointment may include improving pancreatic microcirculation, inhibiting inflammatory reactions, promoting intestinal peristalsis, and relieving pain.

Selection of scales

The trial includes objective indicators such as abdominal circumference, the time of first bowel movement, and evacuation, as well as subjective indicators such as VAS score and APACHE-II score. Those can reflect the efficacy of Yi-Dan ointment in multiple ways. Abdominal circumference can reflect the amount of ascite. The presence of evacuation and bowel movements indicates recovery of gastrointestinal function. VAS is a scoring method used to evaluate the pain degree which is simple, effective, and sensitive. It is commonly used for evaluating pain degree in clinical practice. APACHE-II is the most widely used non-specific scoring system for serious illnesses worldwide. The higher the score, the more severe the disease, the worse the prognosis, and the higher the rate of death.

Selection of detection indicators

The severity of AP is closely related to the extent of the systemic inflammatory response, and certain markers like TNF- α , IL-6, and CRP are strong indicators of AP and early mortality [25]. TNF- α is an important inflammatory factor that directly mediates the inflammatory reaction [26]. It can also trigger the synthesis and release of multiple cytokines such as IL-1 and IL-6, and activate NF- κ B and JNK signaling pathway [27]. It can disrupt microcirculation, inhibit fibrinolysis, stimulate cytotoxicity, and damage the pancreas, and is closely related to early mortality [25, 26, 28]. Elevated serum CRP levels are associated with increased pancreatic injury and the body's response [29]. IL-6 and CRP are commonly used indicators of AP in clinical practice [30]. IL-6 is closely related to the severity of AP. IL-6 can prolong the inflammatory process and affect the repair of pancreatic injury [31]. In the early stages of AP, IL-6 levels can be used to predict the development of AP and serve as a marker of AP severity [32, 33]. It can stimulate the synthesis of acute phase proteins, increase the production of bone marrow neutrophils, promote B cell growth, and antagonize regulatory T cells [34]. PCT is also a reliable laboratory test to predict infections and the clinical severity [35]. CT-scan can help to identify early complications [36]. Compared with individual biomarkers, the combined detection of WBC, CRP, PCT, IL-6, IL-10, TNF- α and CT has a higher diagnostic value for judging the severity of AP. The use of multiple serologic indicators for assessment provides a more accurate classification and prognosis of AP [33].

In conclusion, on the basis of early clinical application, we infer that the external application of Yi-Dan ointment in combination with basic treatment can expedite the relief of abdominal pain and distension, shorten the time to first bowel movement and evacuation, and reduce CT scores and inflammatory factor levels in AP patients when compared to basic treatment alone. We hope that the results of this trial will prove the clinical efficacy of Yi-Dan ointment and contribute to enhancing the range of treatment options available for AP.

Conclusion

This protocol is about the treatment of acute pancreatitis with external application of Yi-Dan ointment. The trial results will provide high-quality evidence for Yi-Dan ointment, and provide a complement to existing treatment options for pancreatitis.

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