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STUDY PROTOCOL

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Analysis of the effect of the Xianglian capsule on patients with diarrhea after cholecystectomy: a protocol for a single-center, randomized controlled trial

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Abstract

Introduction Diarrhea is a common complication in patients after cholecystectomy. In China, tens of millions of patients experience diarrhea every year after cholecystectomy, which results in long-term pain in patients. Traditional Chinese medicine is a national treasure and has made great contributions to human health throughout the long history of the Chinese nation. However, as a classic ready-for-use traditional Chinese medicine, the exact clinical efficacy of the Xianglian preparation needs further observation. This article presents the protocol of a single-center, randomized controlled trial to evaluate the clinical efficacy of Xianglian capsules in patients with diarrhea after cholecystectomy.

Methods and analysis This study was conducted in the Department of Hepatobiliary and Pancreatic Surgery, Second Affiliated Hospital of Guangdong Medical University, following the recommendations of the current SPIRIT and CONSORT statements. We will recruit 90 patients who have developed diarrhea after cholecystectomy and randomize them 1:1 into the observation and control groups. The control group was given starch placebo capsules, and the observation group was given Xianglian capsules. Patient diarrhea-related indicators were collected at baseline and 5 days postdose. We will also collect patients' intestinal inflammation-related indicators and fecal microbial samples to analyze the possible mechanism of action of drugs.

Discussion This study will clarify the clinical effects of the Xianglian preparation on patients with diarrhea after cholecystectomy, provide evidence-based evidence, and promote the development and application of this classic prescription.

Trial registration http://www.chictr.org.cn. Trial number: ChiCTR2200061854. Registered on 04 July 2022.

Keywords Xianglian capsule, Diarrhea, Randomized controlled trial, Traditional Chinese medicine

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Strengths and limitations of the study

This study is a single-center, nonblind, randomized controlled trial to evaluate the efficacy of the Xianglian capsule in the intervention of patients with diarrhea after cholecystectomy.

This study explored the mechanism of the use of the Xianglian capsule in the treatment of diarrhea patients after cholecystectomy, which may promote the development of traditional Chinese medicine.

The relatively small sample size of the study may affect the generalizability of the results.

The absence of blinding in the study design could introduce bias.

This study only observed the short-term efficacy of the drug and lacked an assessment of the long-term efficacy.

Introduction

At present, the incidence of cholelithiasis in the Chinese population can reach 7%−10%, and gallstones account for more than 50% of cases. The incidence of new diarrhea is 25% one week after cholecystectomy and 5.7% three months after cholecystectomy [1]; that is, approximately 5.18–32.5 million patients experience diarrhea after cholecystectomy every year. However, the quality of life of patients who develop chronic diarrhea is greatly reduced, which can even cause a greater social burden [2]. The occurrence of diarrhea may be related to changes in the rhythm and flow of bile into the intestinal tract and malabsorption of bile acids after cholecystectomy [3–6].

As bile continues to enter the intestinal tract, the unabsorbed bile acid components increase, especially deoxycholic acid and chenodeoxycholic acid, which can stimulate the secretion of water and electrolytes from the intestinal mucosa and promote increased intestinal peristalsis [7]. After fatty foods are eaten, a lack of bile to assist in digestion and absorption can lead to steatorrhea [8]. After cholecystectomy, patients experience an imbalance in bile acid metabolism. Moreover, due to the lack of gallbladder surface protein D, the number of intestinal T cells decreases sharply, causing immune abnormalities [9]. In addition, the small intestinal fluid layer is weakly alkaline, the pH is 8–9, and normal bile is weakly acidic. Its pulse secretion is beneficial for shaping a good intestinal microecological environment and maintaining the stability of the intestinal pH value [10]. After cholecystectomy, bile is continuously secreted, which affects the acid–base balance in the intestinal tract and subsequently affects the living environment of some flora. An imbalance in bile acid metabolism, immune abnormalities and acid–base imbalances can change the intestinal microenvironment, leading to changes in the intestinal microbial flora [11]. The intestinal flora is a rich and complex microbial community. The intestinal tract of a normal adult contains 300–500 different kinds of bacteria, which can synthesize a variety of microorganisms and essential amino acids necessary for human growth and development [12]. In general, the host maintains the homeostasis of the intestinal environment. Disruption of this homeostasis (an imbalance in the intestinal flora) leads to the occurrence of disease, which leads to the most direct diarrhea in patients after cholecystectomy.

Traditional Chinese medicine is a national treasure and has made great contributions to human health throughout the long history of the Chinese nation. As a classic ready-for-use traditional Chinese medicine, the Xianglian preparation can clear away heat and dry dampness, promote qi, relieve pain, and is used for diarrhea and abdominal pain, which turns yellow and sticky; Damp-heat dysentery, tenesmus; Abdominal pain and diarrhea; Bacillary dysentery, enteritis [13–15]. Liu Chang-Shun et al. used a combination of network pharmacology and pharmacokinetics to study and confirm the inhibitory effect of a Xianglian preparation on the JAk2-stat3 pathway and then provided a theoretical basis at the molecular level for its anti-inflammatory effect [16]. Our research group also conducted animal experiments in the early stage to confirm that the Xianglian preparation has beneficial effects on the intestinal flora [17]. In addition, wood incense in the Xianglian preparation can relieve pain, strengthen the spleen and eliminate the stomach. On the one hand, mutandis in mice has the pharmacological effects of promoting gastrointestinal motility and gastric emptying; on the other hand, it may effectively promote the absorption of pepsin in the small intestine and maintain the activity of pepsin to reach the astringent intestine and stop diarrhea [18]. In our clinical work, we found that some patients experienced diarrhea after cholecystectomy, and the diarrhea of patients improved after receiving the Xianglian preparation ready-for-use traditional Chinese medicine. However, the exact clinical efficacy of the Xianglian preparation needs further observation, and whether the therapeutic effect of the Xianglian preparation is related to regulating and interfering with bile secretion, reducing bile enterohepatic circulation and intestinal peristalsis, protecting the intestinal mucosa, balancing the intestinal pH value, and improving diarrhea caused by cholecystectomy needs further study.

Therefore, this study aimed to use the Xianglian capsule to intervene in patients after cholecystectomy, clarify the therapeutic effect of the Xianglian capsule on patients with diarrhea after cholecystectomy, and explore the mechanism by which the Xianglian capsule alleviates diarrhea after cholecystectomy.

Methods and analysis

Study design

This project describes a single-center, randomized controlled trial protocol with a patient number of 90 and an allocation ratio of 1:1, where the observation group (XL group) was given Xianglian capsules and the control group (SP group) was given Starch placebo capsules to assess the clinical efficacy of Xianglian capsules in patients with diarrhea after cholecystectomy and to preliminarily explore the possible mechanisms of action. The protocol (Version number: The Second Affiliated Hospital of Guangdong Medical University 1.1 Special Edition, Version Date: 2022–05–09) adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement [19] (see the attachment for details: SPIRIT_checklist). We are recruiting participants at the Second Affiliated Hospital of Guangdong Medical University. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangdong Medical University (Approval No. PJKT2022-015–01).

Recruitment

All patients who undergo laparoscopic cholecystectomy will be informed of common postoperative complications, including diarrhea, and patients with diarrhea will be invited to participate in the study. Recruitment advertisements will be posted at the entrance to the doctors' workstations and nurses' workstations in the Department of Hepatobiliary and Pancreatic Surgery, and the chief physician, who is a member of the project team, will be responsible for explaining the study to patients (for details, please refer to the attached materials: Clinical Subject Recruitment).

Eligibility criteria

Inclusion criteria

The inclusion criteria will be as follows:

1. All patients with diarrhea one week after undergoing laparoscopic cholecystectomy
2. Age between 18 and 65 years.
3. Voluntarily participated in the experiment and signed the informed consent form.

Exclusion criteria

The exclusion criteria will include the following:

1. Diagnosis of infectious diarrhea or a history of chronic diarrhea
2. The presence of diabetes mellitus; hypertension; and serious organic lesions of the heart, liver, kidneys and other vital organs.
3. Accompanying other autoimmune diseases
4. Antibiotics, microecological agents, and immunomodulatory and gastrointestinal stimulants were used for half a month prior to treatment.
5. Pregnant, lactating patients.
6. Participating in other experiments.
7. Allergies and hypersensitivity to the drug.
8. Those who were not suitable for the Xianglian capsule according to a Chinese medicine diagnosis were included.

Shedding criteria

The shedding criteria include the following:

1. Out of contact.
2. Died of other diseases.
3. Unwillingness or other reasons for not being able to continue with the experiment.

The general clinical data, including sex, age and severity of the disease, were matched between the two groups, and the difference was not statistically significant ($p > 0.05$).

Study procedure

In the first step of the study, a complete medical history was obtained from each patient. The recruiter subsequently explained the study procedures, risks and benefits and supplied the patient with a leaflet containing the study's description. Next, patients signed an informed consent form if they were interested in joining the study and were ≥ 18 years of age. Following this, patients eligible for enrollment will be randomized via a numerical table method (for details, please refer to the attached material: subject randomization procedure). All signed informed patients will be asked to collect fecal samples for measurement of the fecal Ph. All enrolled patients will have relevant preoperative laboratory markers collected (the specimen collection operation is detailed in the attachment standard procedure for specimen collection), laboratory tests will be performed at baseline and at the end of the study, and clinical symptoms will be collected during daily telephone follow-up after enrollment [20].

The Consolidated Standards of Reporting Trials flow diagram is shown in Fig. 1, and the study procedures and time points are shown in Table 1.

Diagnose

The diagnosis of diarrhea in Western medicine is as follows: changes in stool properties; thin stools (loose,

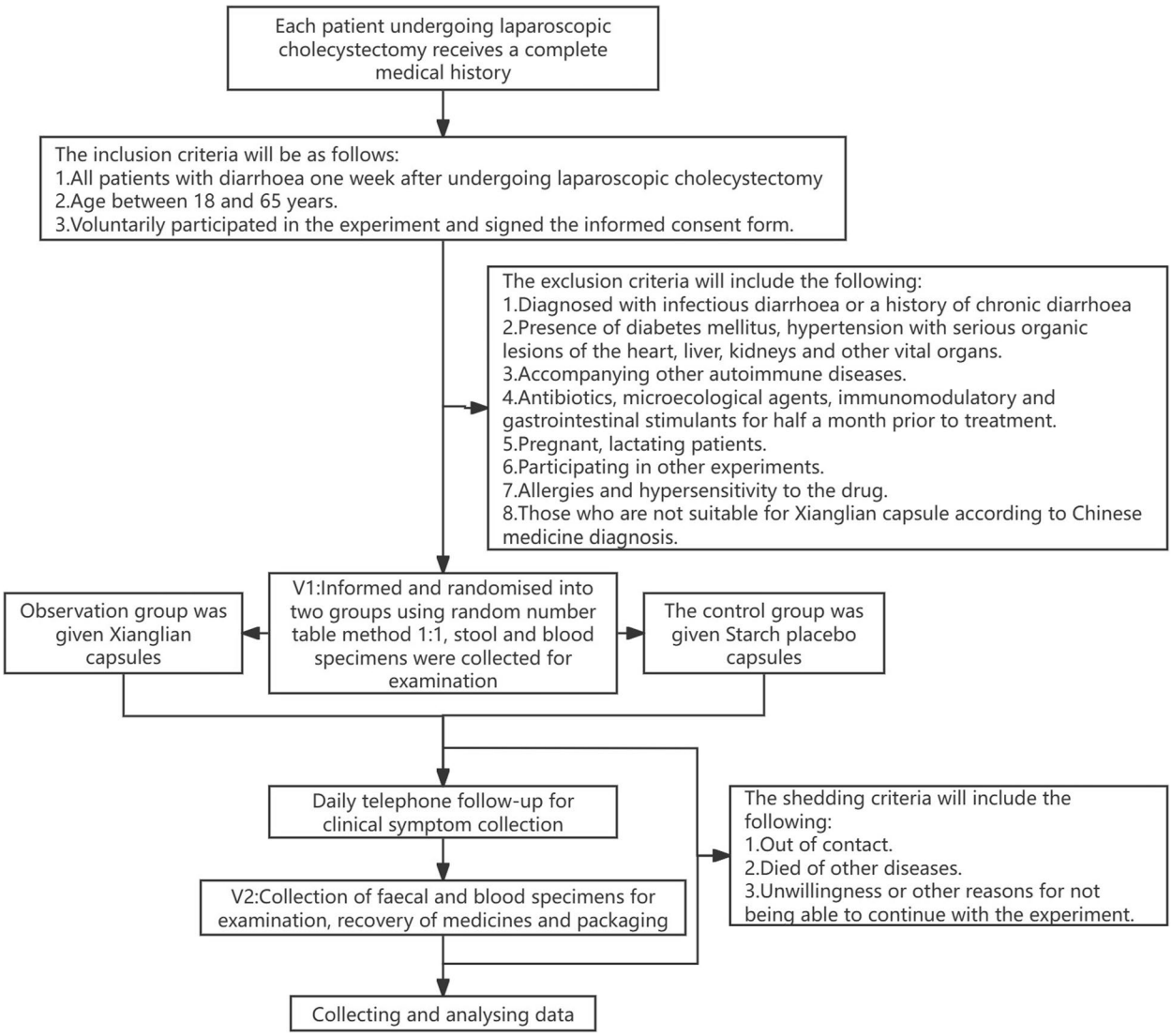

Fig. 1 Consolidated standards of reporting trials flow diagram

Table 1 Procedures carried out during the study

Type examination/test	Time point
Infection indicators, selected Inflammation indicators	preoperative, 7 ± 1 days postoperatively (day 0, i.e., prior to dosing)
fecal routine, Fecal pH	preoperative, 7 ± 1 days postoperatively (day 0, i.e., prior to dosing) and 5 days postdose
Inflammation indicators and fecal microorganisms	7 ± 1 days postoperatively (day 0, i.e., prior to dosing) and 5 days postdose
Clinical symptom(Stool characteristics, frequency, stool volume, abdominal pain score, number of bowel sounds per minute)	After enrollment, patients were self-monitored on a daily basis until symptoms disappeared or until 3 weeks after full surgery

Infection indicators include Blood routine, Procalcitonin, C-reactive protein. Inflammation indicators include Interleukin 2 (IL-2), Interleukin 4 (IL-4), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Interleukin 10 (IL-10), Interleukin-1β (IL-1β), Human tumor necrosis factor alpha (TNF-α), Human transforming growth factor beta (TGB-β), Human gamma interferon (IFN-γ)

watery, mucopurulent or pus-blood stools); and a frequency of defecation ≥ 3 times/day, accompanied by an increase in the volume of defecation (> 200 g/d) [21, 22].

The diagnostic criteria for diarrhea in Chinese medicine are as follows: 1) Increased frequency of stools, more than 3 times a day, loose or watery stools, and increased

stool volume. 2) Symptoms persist for more than 1 day. 3) Types of diarrhea to be certified by a Chinese medicine practitioner [23].

Intervention

In the observation group, after diagnosis by a Chinese medicine practitioner, oral administration of 2 capsules of Xianglian capsules 3 times a day was prescribed by the Chinese medicine practitioner, and the duration of treatment was 5 consecutive days or 1 day after complete disappearance of diarrhea symptoms.

The control group was the same as the intervention group except for oral placebo capsules.

Drug information

Xianglian capsules (Approval Number: National Drug Approval Number Z10930038, Specifications: 0.55 g10 capsules, Manufacturer: Li Shizhen Pharmaceutical Group Co., Ltd., Main Ingredients: Coptis (processed with Wu Zhu Yu), costus. Keywords: starch, talcum powder, magnesium stearate. Functions and Indications: Clearing heat and drying dampness, promoting qi circulation and relieving pain. The patient was used for diarrhea, abdominal pain and sticky yellow stool. Oral administration, 2–3 capsules each time, three times a day).

Placebo treatment

The placebo capsule is made of 100% corn starch, which is filled into an empty capsule shell with the same shape as Xianglian capsule, and is produced and provided by Yuan Lujiang's research group.

Adverse events reporting

Adverse events will be recorded from signed consent until the 30-day follow-up phone call after the V2 visit [24].

Participant compliance

Participants will bring empty packages of the medication they are taking and take the remaining study medication at the second visit. Medication adherence will be counted in conjunction with the medication recordings from the daily telephone follow-up visits.

Clinical outcomes

Assessment of treatment effect:

1. Clinical recovery: the number, volume and characteristics of stools returned to normal; no discomfort during defecation; disappearance of accompanying symptoms and signs; and a normal laboratory examination.

The laboratory examination was normal.

2. Obvious effects include the following: the number of stools is 2–3 times a day, the stools are almost formed, the stools are loose only once a day, and the discomfort of defecation is obviously improved.

The total score of accompanying symptoms and signs was reduced by more than 70% compared with that before treatment. The laboratory test results significantly improved.

3. In terms of effectiveness, the shape, frequency and quality of stools have improved, the total score of accompanying symptoms and signs has been reduced by more than 35% compared with the pretreatment level, and laboratory tests have improved.
4. Ineffective: Failure to meet the above criteria.

Overall effective rate = (number of clinically cured cases + number of apparently effective cases + number of effective cases)/total number of cases × 100%. The changes in symptom scores before and after treatment in both groups, including stool properties and stool frequency, which were classified as none, mild, moderate or severe according to the severity of the disease, were observed, and the detailed symptom score assignments are shown in the Appendix—Subject Visit Card and Subject Telephone Follow-up Slip [23].

Patient and public involvement

Patients and the public were not involved in the development of this study protocol.

Sample size

In this study, a two-tailed test was used, the effect size was set at 0.8, the significance level a (class I error) was 0.05, and the power 1-B (class I II error) was 0.9. According to the sample ratio of the XL group to the SP group of 1:1, the allocation calculation shows that at least 34 samples are needed for each of the two groups, and at least 68 samples are needed for the two combinations. Considering that approximately 25% of the patients were excluded or dropped out, 45 patients (90 total) were enrolled in each group [25, 26].

Statistical analysis

All the statistical tests were conducted through two-tailed tests, and a p value ≤ 0.05 was considered statistically significant for the difference being tested [27]. The description of quantitative indicators will be used to calculate the number of cases, means, SDs, medians and IQRs. The classification indicators are used to describe

the number of cases and percentages (frequency and frequency rate) [28].

Data collection and handling

Identification numbers will be given to all participants. We used the FREE Electronic Data Capture System (version 1.0; Beijing, China) for clinical data collection and database construction. The required sociological, clinical and laboratory information will be obtained from the hospital information system [28]. Clinical efficacy-related data will be collected and recorded on CRFs (please refer to the attachment for details, including the subject information card, subject visit card and subject telephone follow-up sheet).

Ethics and dissemination

The study was funded by the Guangdong Provincial Bureau of Traditional Chinese Medicine (Project Number: 20221439) and approved by the Ethics Committee of the Second Affiliated Hospital of Guangdong Medical University (Approval No. PJKT2022-015–01)). Written informed consent will be obtained from all trial participants or their legal representatives. Consent will be voluntary and free from coercion, and participants are free to withdraw at any time without this affecting their future care (for details, please refer to the attachment: Informed Consent). The confidentiality of participants will be protected at all times (for more details, see the Confidentiality Agreement). The results will be published in peer-reviewed journals and disseminated via presentations at international conferences. The study was registered at the China Clinical Trial Center on July 04, 2022 under the registration number ChiCTR2200061854.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12906-025-04831-z.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.

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Authors' contributions
SG and PC contributed to the study conception and design, writing (including draft, review and editing) and finalization of the manuscript. DC and SD reviewed the manuscript. SG and SD contributed to conceptualization, supervision, article drafting and final approval of the version to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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