Effect of Zangfu ointment and massage therapy on functional constipation: a protocol for a randomised controlled trial

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Author contributions
Xiao-Na Zhang wrote the article, Hong-Jie Cheng provided the article ideas and revised and polished the article, Nai-Wei Zhang and Bo-Yi Jia conducted literature search and data collation, Li-Bao An and Wei-Fang Liu conducted literature screening. Bao-Tuan Zhao supervised the project implementation.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
FC, Functional Constipation; TCM, Traditional Chinese Medicine.

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Abstract
Introduction: Functional Constipation (FC) is a type of functional bowel disease that is in Clinically characterized by dysportia, decreased frequency of bowel movements, or incomplete bowel movements in the absence of irritable bowel syndrome symptoms, at least 6 months before diagnosis, and symptoms within the last 3 months. At present, commonly used drugs include enema and suppositories, laxatives, microecological preparations, gastrointestinal motility drugs and other treatments. However, the effect is limited. Traditional Chinese medicine (TCM) treatment of FC has advantages.

Methods: In this randomized controlled study, 244 eligible patients were randomly assigned in a 1:1 ratio to a treatment group (Zangfu ointment and massage therapy + Lactulose Oral Liquid) and a control group (Lactulose Oral Liquid) for 14 days. Number of spontaneous defecation per week and first defecation time will be used as primary outcomes, and Traditional Chinese Medicine (TCM) syndrome scores and syndrome scores, PAC-QOL form will be used as secondary outcomes. Blood routine, liver function, and renal function will be used as safety outcomes. The primary and secondary outcomes will be performed at 0th, 7th, and 14th day, and the safety outcomes will be performed at 0th and 14th day.

Ethics and dissemination:
Ethical approval has been obtained from the Committee on Health Research Ethics of the Fangshan Hospital, Beijing University of Chinese Medicine, Beijing, People’s Republic of China (FZY LK-2020-010) on September 18, 2020. All patients will be provided oral and written information about the trial before screening. The study results will be disseminated by peer-review publications and conference presentations.

Trial registration number: ChiCTR2000038754 (registered on April 14, 2021).
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STRENGTHS AND LIMITATIONS OF THIS STUDY
(1) The efficacy of the Zangfu ointment and massage therapy is evaluated in a randomised, double-blind 2-week clinical trial in FC patients.
(2) Form a complete and generalizable regimen for the treatment of FC (Qi stagnation) with the Zangfu ointment and massage therapy

Keywords: functional constipation; Zangfu ointment and massage therapy; Qi stagnation; a randomized; controlled clinical trial
Introduction

Rome IV. pointed out that the prevalence of chronic constipation in adults ranges from 1.9%–40.1%, with an average of about 14% [1]. Results of a bulk (41,724 respondents) survey of Australian women showed the incidence rate of self-reported constipation is 14.1% in young women (18–23 years old) and 26.6% in middle-aged women (45–50 years old), 27% for older women (70–75 years old) [2]. The natural history of FC is currently unknown. One study found 89% of adult patients still have symptoms 12–20 months after initial diagnosis. Large population studies show During the 12-year follow-up period [3], 77.8% of patients (N = 1365) had symptom relief [4], more than 20 years follow-up period, only 3% of patients (N = 2835) had persistent constipation, but the other 21% had intermittent constipation [5]. Surveys conducted in adults in the United States evaluated patients’ perceptions of chronic constipation, the occurrence of common symptoms, the frequencies were: straining to defecate (79%), dry stool (71%), abdominal discomfort (62%), bloating (57%), decreased frequency of bowel movements (57%) and incomplete bowel movements (54%) [6]. Risk factors for FC include gender and energy decreased intake and increasing age [7, 8]. More meta-analyses suggest, gender, increasing age, socioeconomic status were major risk factor for chronic constipation [9, 10]. Studies had shown that the prevalence of FC in China was about 3%–11% [11]. The incidence of constipation was 6.07% in Beijing and approximately 17.6% in urban Hangzhou [12, 13], and in women Higher than in males [14].

Constipation seriously affects the quality of life of patients, and some chronic constipation may play an important role in the occurrence of colorectal cancer, hepatic encephalopathy, breast disease, Alzheimer’s disease and other diseases. In the case of acute myocardial infarction, cerebrovascular accident, etc., excessive straining to defecate can even lead to death [15–16]. Treatment of FC focused on improving symptoms, smoothing stools, and restoring normal bowel regularity. Western medicine treatment includes basic treatment and drug treatment. Basic treatment is preferred, it mainly includes changing eating habits and treating patients psychologically, physiologically, and behaviorally. For those who do not respond to basic therapy, pharmacologic intervention may be considered. At present, commonly used drugs include enema and suppositories, laxatives, microencephalonic preparations, gastrointestinal motility drugs and other treatments. However, long-term use of laxatives has found that long-term use of laxatives can produce electrolyte imbalance, laxative dependence, nerve damage to the intestinal mucosa, and in severe cases, adverse reactions such as colonic melanosis [17].

The disease of FC in TCM is called constipation, which is often caused by emotional disorders, poor drinking, post-illness, postpartum, old age and weakness, drugs and others. Its disease is located in the large intestine, and the liver, lungs, dysfunction of the spleen, stomach, and kidney organs. The basic pathogenesis is unfavorable colonic depapsulation and conduction loss [18]. With the continuous in-depth research of traditional Chinese medicine on the etiology and pathogenesis of FC and the use of differentiated drugs, the treatment of constipation in traditional Chinese medicine is mainly divided into oral drug treatment and in vitro therapy. However, oral Chinese medicine laxatives, such as rhubarb, contain anthraquinones, which can easily cause colonic melanosis [19], so they should not be taken for a long time. In vitro therapy mainly includes acupuncture, auricular thread lifting, auricular therapy, enemas, acupressure point application, ointment, etc. Because of the advantages of simple and easy implementation and quick effect, in vitro therapy is widely used by patients.

The Zangfu ointment and massage therapy is a combination of ointment and massage [20], which is that the operator applies the ointment to the stomach and massages the abdomen with a heated massage instrument. When using the Zangfu ointment and massage therapy to treat diseases, First of all, the ointment made by special technology is evenly applied to specific acupuncture points, meridians or skin surfaces, as the medium of massage, on the one hand, it plays a lubricating role and prevents massage from damaging the skin; On the other hand. The ointment is applied directly to the local skin, under the action of massage, the active ingredients of the drug are fully absorbed by the skin, enter the blood circulation, directly reach the patient, avoid the gastrointestinal absorption process, and reduce the impact of the drug on liver and kidney function [21]. The combination of massage techniques and ointment application not only enhances the effect of the technique, but also improves the penetration effect of the drug, giving full play to the role of activating blood and removing stagnation, resolving stasis to stop pain, and adjusting the function of internal organs.

Methods and analysis

Design

The trial is rater-blinded, randomized controlled, which conducting an 14-day. The treatment group (Zangfu ointment and massage therapy + Lactulose Oral Liquid) and the control group (Lactulose Oral Liquid) will be compared to observe the effect of the Zangfu ointment and massage therapy on the FC patients, and to evaluate its safety. The trial will be carried out in the Gastroenterology Department of the Fangshan Hospital of Beijing University of Chinese Medicine. All participants are required to provide written informed consent prior to entry into the trial. The research flow chart is shown in Figure 1.

Ethic approval

This protocol was carried out in accordance with the principles of the Declaration of Helsinki, and it has been approved by the Ethics Committee of Fangshan hospital, Beijing University of Chinese Medicine (approval number: FZY LX-2020-010) and the whole process was follow up. The study were registered in Chinese Clinical Trials Registry (registration number:ChiCTR2000038754).

Participants

All 244 patients are FC (Qi stagnation constipation, gas operation is blocked) patients who are admitted to the outpatient clinic and ward of the Spleen and Gastroenterology Department of our hospital through the poster open recruitment. Participants who meet the research criteria will be invited to the Andrology Department of Fangshan Hospital, Beijing University of Chinese Medicine for the research. Eligible participants will be randomized 1:1 to treatment and control groups. The treatment will last 14 days.

Diagnostic criteria. The diagnostic criteria of FC will be formulated by the “ROME IV: Functional Gastroenterology/Brain-Gut-Interaction Abnormalities” developed by the American Board of Gastroenterology. Specifically:
Diagnostic criteria of Western medicine

1. Must include 2 or more of the following:
   a. More than 1/4 (25%) of bowel movements feel strenuous;
   b. More than 1/4 (25%) of defection is dry bulb feces or hard feces (Bristol fecal trait scale type 1–2);
   c. More than 1/4 (25%) have a feeling of incomplete bowel movements;
   d. More than 1/4 (25%) bowel movements have anorectal obstruction/blockage;
   e. More than 1/4 (25%) of bowel movements require manual assistance (such as finger assistance with defection, pelvic floor support);
   f. Symptoms have been present for at least 6 months before diagnosis, and meet the above diagnostic criteria in the last 3 months.
   *FC is not diagnosed for research purposes if the patient meets the diagnostic criteria for opioid-induced constipation.

TCM Differentiation Standards

Using the dialectical classification of constipation in the "Consensus Opinions of Experts on the Diagnosis and Treatment of Constipation in Traditional Chinese Medicine (2017)," the dialectical criteria for Qi stagnation constipation are as follows:

Main symptoms: (1) unpleasant defection; (2) bloating;
Secondary symptoms: (1) bowel ringing; (2) chest and flank fullness; (3) hiccups or sagittal frequency;
Tongue veins: dark red, thin moss, veined strings.
Symptom diagnosis: 2 main symptoms, 2 secondary symptoms, refer to the tongue pulse, can be diagnosed.

Inclusion criteria. The inclusion criteria are as follows: Diagnostic criteria for FC in ROM IV; Standards of syndrome differentiation of Qi stagnation syndrome; Aged 18 to 75 years; Having not been taking any laxative drugs before enrollment; Clear consciousness, good general condition, can cooperate with examination and treatment; Volunteer to participate in the research and sign the informed consent.

Exclusion criteria. The exclusion criteria are as follows: Allergic to known Chinese herbal medicines; Breastfeeding or pregnant women; Abdominal skin damage or skin disease; Constipation caused by tumors, inflammation, endocrine and metabolic diseases, and drugs; Patients with coagulation dysfunction or those who have been using anticoagulants such as warfarin and heparin; Combined with serious heart, liver, kidney damage or serious cognitive dysfunction, unable to cooperate with examination and treatment.

Sample size

Check the literature to find out, the average bowel frequency for 14 days of lactulose treatment was 4.4 ± 1.6 times per week. The frequency of bowel movements after visceral ointment therapy was 5.0 ± 1.46 times per week. In this study, the Class I error α is controlled at 0.05 (bilateral), and the test performance β is 0.2. The distribution ratio of the samples between the treatment group and the control group was 1:1, and the effective sample size of each group required 102 cases. The sample size included in this study met the criteria for follow-up studies. Considering the dropout of cases and assuming a loss-to-follow-up rate of 20%, the final sample size is 244 cases, with 122 people in the treatment group and 122 in the control group.

Randomization and blinding

We use Excel to generate a sequence of random numbers, number based on the generated random numbers, and then sort the random numbers, the number of the two groups is assigned 1:1, the 122 numbers with the large random numbers are assigned to the experimental group, the small 122 numbers are assigned to the control group, and finally the assigned serial number is put into an opaque envelope and numbered on the envelope, and the number on the envelope is consistent with the random number number. All envelope information is kept by a dedicated person.

Interventions

Treatment group

Treatment options: Zhangfu ointment and massage therapy + Lactulose Oral Liquid.

Composition of the ointment drug: Dahuang (Rhei Radix et Rheum) 40 g, Zhishi (Aurantii Fructus Immaturus) 30 g, Houpo (Magnoliae officinalis Cortex) 20 g, Wyuao (Linderae Radix) 10 g, Binglang (Arecae Semen) 10 g, Taoren (Persicae Semen) 10 g, Danggui (Angelicae Sinensis Radix) 10 g, Muxiang (Aucklandiae Radix) 10 g.

Method of the ointment drug: All of the above Chinese medicines are respectively dried, the drying temperature was 60–90 °C, and the drying time was 10–20 minutes (the drying time was changed due to humidity). The dried medicinal materials are crushed first, and then crushed at low temperature at a temperature of 8 °C, crushed to a particle size of 200 mesh, crushed, mixed and packaged.

The above production is completed by the Department of Pharmacy of our hospital, placed in the Chinese medicine treatment room of the ward, and stored at room temperature.

Method of the ointment preparation: The paramedic take 400 mL of petroleum jelly and heat it in a microwave over medium heat for about 9 minutes to melt petroleum jelly into a liquid state. The paramedic take 200 g of mixed Chinese medicine powder, add it to liquid petroleum jelly, stir repeatedly for 10 minutes to make a paste, let stand for 90 minutes, solidify into a paste, and set aside.

The above production is prepared by our fixed paramedic in real time.

Steps:
   1. Prepare the ointment;
   2. Preheat Massage instrument, The initial regulation temperature is 60 °C;
   3. The patients are instructed to take the supine position, expose the abdomen, select the corresponding acupuncture points, and cover the subject's lower abdomen with a treatment napkin;
   4. An appropriate amount of ointment is applied to the Shenque, and the temperature of the massager is adjusted appropriately according to the tolerance of the subject;
   5. The operator holds the massage instrument, exerts force with the wrist, the depth of compression is determined according to the subject’s tolerance and fat thickness, the pressing acupuncture points start from the Shenque, and then pass through the Qihai, Guanyuan, Tianzhu (right), Zhongyu Acupoint, Tianzhao (left), and then to the Qihai, continuously rotate clockwise for 15 min, and end at Tianzhu (left);
   6. The operator pays attention to asking the patient’s feelings during the operation, and adjusts the strength and temperature in time;
   7. At the end, Wrap plastic wrap over abdominal plaster and keep it warm for 2 hours during the ointment, pay attention to the patient's skin.

Treatment Cycle: 5 days of continuous treatment, 2 days of rest, for one course of treatment, 2 courses of continuous treatment. Lactulose Oral Liquid (100 mL/bottle), produced by Beijing Hanmei Pharmaceutical Co., Ltd., 15 mL/time, once a day, oral, takes in the morning.

Control group

Medicinal use: Lactulose Oral Liquid (100 mL/bottle), produced by Beijing Hanmei Pharmaceutical Co., Ltd., 15 mL/time, once a day, oral, takes in the morning.

Treatment cycle: 5 consecutive days of oral administration, 2 days of rest, one course of treatment, 2 consecutive treatments.

Combined treatment regulations

If the subjects meet the inclusion criteria, and the patients with other diseases need to continue to use the drug in the clinical trial, or if they
really need to add other drugs or treatment methods due to the needs of the disease treatment, the drugs used should be recorded in the case report form (CRF) in detail. The drugs and treatment methods that must be taken in combination with other diseases must be recorded in detail in the combined medication table. The patients record in detail adverse events, side effects or adverse drug reactions that occurred during the study in the patient log card, such as diarrhea, fecal incontinence, abdominal pain, allergies, etc.; And before and after treatment, blood routine, liver and kidney function will be detected. The patient will be asked to complete relevant examinations and assessments as much as possible, and the case will be considered an excluded case.

Outcome measures

Primary outcomes
Number of spontaneous defecation per week and First defecation time will be used as primary outcomes. Number of spontaneous defecation per week will be used as the main indicators of this study, and will be detected on 0th, 7th, 14th day. First defecation time will be used as the main indicators of this study, and will be detected on 7th day.

Secondary outcomes
Traditional Chinese Medicine (TCM) symptom scores and syndrome scores, PAC-QOL form will be used as a secondary outcomes. TCM symptom scores and PAC-QOL form will be tested on 0th, 7th and 14th day. Syndrome scores will be tested on 0th and 14th day.

Safety outcomes
Blood routine, liver function, and renal function will be used as safety outcomes, and will be treated on 0th and 14th day of treatment detection. If an adverse event occurs, the clinical investigator will record it in detail on the CRF (including symptoms, time of onset, duration, examination and results). Serious adverse reactions will be reported to the Ethics Committee of the Fangshan hospital, Beijing University of Chinese Medicine and rescue procedures will be implemented promptly.

Quality control and trial monitoring
In the design of this study, it was considered that possible biases in the study were: (1) selective bias at the beginning of the study due to lax inclusion criteria for the participant population; (2) Measurement bias occurred due to some confounding factors during the study. In view of these possible biases, this study intends to train participants through rigorous training population inclusion criteria for quality control and avoidance of selection bias as much as possible through randomisation protocols; In the study protocol–randomized, controlled research methods–the specificities of the intervention did not allow blinding of investigators, so we set up statistical analysts who were not involved in trial design and conduct and blinded statistical analysis of data to minimize measurement bias.

Quality control for researchers:
1. Personnel qualifications
   (1) Clinical intervention implementation personnel: those who must have the qualification of practicing physician and relevant clinical work experience.
   (2) Clinical evaluators: those who must have relevant clinical research experience.
   (3) Data entry personnel: those with medical background and familiar with routine computer operators.
   (4) Quality inspectors: those with relevant work experience.
2. Personnel training
   According to the requirements of the research work manual, relevant training is provided to the personnel involved in the research.

Statistical analysis
Statisticians are separated from research implementers, and specialized statisticians are responsible for data analysis. Statistical analysis of data using SPSS22.0 software. For metrological data, the mean ± standard deviation (t ± s) is used, the independent sample t-test is used for those that conform to the normal distribution, and the nonparametric test is used for those that do not conform to the normal distribution. For counting data, the number of examples (percentage) is used to describe, using chi-square test, Fisher exact probability method, rank sum test, etc. All statistical tests were double-sided, with a statistically significant difference of P < 0.05.

Obtaining informed consent
We develop a plan for the protection of subjects’ rights and interests in accordance with the rights and obligations of subjects stipulated in the Declaration of Helsinki; The research plan will be submitted to the ethics committee for review and implementation after approval. Before initiating a clinical intervention, the investigator must make the subject fully aware of the nature, purpose, possible benefits, and risks of the study on a fully voluntary basis, the “informed consent form” can only be started.

Discussion
The high incidence of FC and the difficulty of treatment seriously affect people’s quality of life. Treatment of FC focuses on improving symptoms, smoothing stools, and restoring normal bowel regularity. Studies have found that long-term use of laxatives can produce electrolyte disorders, laxative dependence, nerve damage to the intestinal mucosa, and in severe cases, adverse reactions such as colonic melanosis [17].

Based on the theory that “Poor colony of the large intestine, loss of conduction”, air conduction is a necessary condition to ensure smooth bowel movements. The ointment is derived from Xiao Cheng Qi Soup and Si Mo Soup. Modern pharmacological studies have shown that Rheubarb can reduce the level of troponoid in the body's smooth muscle, relieve its inhibitory effect on actin filament movement, and promote the movement of the gastrointestinal tract [22]. The flavonoids in citrus aurantium can thrive smooth muscle increases the voluntary movement of the intestinal tubes, and can also promote gastrointestinal motility by regulating gastrointestinal hormones in the body [23], the extraction site of ethyl acetate in Magnolia can enhance the gastrointestinal motility function of hydrochloric acid-induced mice, promote the rate of small intestinal advancement and reduce the rate of ulceration [24]. Wu Yang medicine has antagonistic acetylcholine contraction effect, improves small intestinal tension, and achieves the effect of exhaustion and defecation [25], Betel nut can increase gastrointestinal smooth muscle tone and secretion of digestive juices, promote intestinal peristalsis, and achieve laxative effect [26], the fatty oil contained in peach kernels plays a role in lubricating the intestines [27], Angelica polysaccharides increased the water content of the colon and feces of model mice, and angelica oil shortened the time of bowel movements in mice [28], Xylophylhum promotes small intestinal motility by binding to M choline receptors, but exerts an inhibitory effect on the abnormal hyperpropulsion of the small intestine caused by neostigmine [29]. Massage promotes the absorption of the drug and enhances the effect of drug absorption. Number of spontaneous defecation per week and First defecation time will be used as primary indicators, and TCM symptom scores and syndrome scores, PAC-QOL form will be used as a secondary indicator to provide more reference for efficacy evaluation. The treatment time is 14 days, including follow-up after treatment, so as to better evaluate the prognosis and observe the adverse reactions

A limitation of this trial is that double-blinding was not possible due to the nature of the intervention. Therefore, we will try to ensure that outcome assessors and data managers are unknown about the allocation scheme. The inclusion and exclusion criteria will be strictly followed to improve the homogeneity of subjects. We hope that this research could provide a new approach to FC treatment.

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