Chinese Classical Prescription(Liang-Xue-Di-Huang Decoction)for Hemohhhoidal Disease:study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Hemorrhoidal disease (HD) is one of the commonest proctologic condition in the general population. Medical therapy for HD has not been formally confirmed due to the inconsistent of results. Liang-Xue-Di-Huang Decoction, a kind of ancient Chinese classical prescription, has been used to treat HD from the 19th century in China. However, clinical research of Liang-Xue-Di-Huang Decoction in the treatment of HD is lack. We designed this study to evaluate the efficacy and safety of Liang-Xue-Di-Huang Decoction in the treatment of HD. Methods/Design: A randomized, controlled, double blind, double-mimetic agent and multicenter trial to evaluate the efficacy and safety of Liang-Xue-Di-Huang Decoction is proposed. HD patients (stage I, Ⅱ, Ⅲ) will be randomly assigned into Liang-Xue-Di-Huang Decoction with the addition of Diosmine mimetic agent, or Diosmine with the addition of Liang-Xue-Di-Huang Decoction mimetic agent. Patients will receive a 7-days treatments and a 7-days follow-up. The primary outcome measure is the French Bleeding Score in 7 and 14 days. The Secondary outcome measures are Goligher Prolapse Score and Quality-of-Life Score in 7 and 14 days. Discussion: This study will provide objective evidence to evaluate the efficacy and safety of Liang-Xue-Di-Huang Decoction in treatment of HD. Trial registration: Chinese Clinical Trial Registry. ChiCTR-1900022531.Registered 15 Apr 2019, http://www.chictr.org.cn/listbycreater.aspx.

Introduction

Hemorrhoidal disease (HD), one of the oldest and commonest proctologic condition in the general population, is more frequent in industrialized countries[1]. The true prevalence of HD in the general population is unknown and probably differents from country to country[2]. In the United States, HD is the third most common outpatient gastrointestinal diagnosis, affecting between 20 to 50% of the population and resulting in 4 million emergency visits annually[3]. Chronic bleeding is the main symptom of HD[4].

Treatments for HD include medical therapies and surgery[5]. Medical therapies for HD have not been formally studied where the results have been inconsistent[3]. Increased fiber and fluid intake has been shown to improve symptoms of mild-to-moderate bleeding [6]. However, the fiber is not recommended as primary treatment to severe bleeding[7]. Another common medical prescription in patients with bleeding hemorrhoids is micronized purified flavonoid fraction. These drugs include diosmin, hesperidin, and cumarin. Each of these treatments has drawbacks, such as mild gastrointestinal disturbances[2]. There is still no evidence from well-designed studies to support the use of any of the over-the-counter preparations[8].

Liang-Xue-Di-Huang Decoction, a kind of Chinese herbal medicine, listed in Table 1, which has been approved by the National Administration of Traditional Chinese Medicine of People's Republic of China in 2018[9]. *Liang-Xue-Di-Huang* Decoction has been used for HD from the 19th century in China with good effects and few adverse events. However, it was still necessary to prove the efficacy and safety of this ancient Chinese classical prescription. The aim of the present study is to evaluate *Liang-Xue-Di-Huang*

Decoction in the treatment of HD using a randomized, controlled, blind and multicenter trial among officially registered Chinese colorectal consultants, fellows and residents in China.

Methods/design

Design

This study is designed as a randomized, controlled, blind and multicenter trial. Trained researchers introduce the trial to patients, give them information sheets and consent forms. All patients have to obtain “Ethics approval and consent to participate” section and give their written informed consents prior to enrolment. The study’s flow chart is shown in Figure 1.

Ethics

The trial protocol is conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki (2008)[10]. Central ethical approval has been confirmed from the group leader's ethic committee of Affiliated Hospital of Nanjing University of Chinese Medicine (ref approval no. 2019NL-158-02) and four sub-centers ethical will comply with the group leader's ethics approval. Written informed consent will be obtained from each patient.

Recruitment

A total of 240 Chinese patients who fulfill the screening criteria will be recruited at five hospitals in China: 1) Group leader, Affiliated Hospital of Nanjing University of Chinese Medicine, will recruit 64 patients through posters, 2) Sub-center, Changzhou Hospital of Traditional Chinese Medicine, will recruit 60 patients through posters, 3) Sub-center, Suzhou Hospital of Traditional Chinese Medicine, will recruit 60 patients through posters, 4) Sub-center, Xuyi Hospital of Traditional Chinese Medicine, will recruit 28 patients through posters, 5) Sub-center, Wujin Hospital of Traditional Chinese Medicine, will recruit 28 patients through posters.

Sample size

According to the literature search results, bleeding was used as the primary outcome measure for the treatment of HD by diosmin. It was estimated that *Liang-Xue-Di-Huang* Decoction treatment is not inferior to that of diosmin treatment. According to the non-inferiority test sample size calculation formula, for a two-sided significance level of 0.05, the standard deviation is 0.4, (α=0.05, β=0.2, δ=0.15), the non-inferiority bound is 0.15 when the degree of grasp (1-β)=80%, the sample size is calculated using the formula: (See Formula 1 in the Supplemental Files)

Considering a 10% loss to follow-up, the sample size is 240 cases (n=120 in each group).

Randomization

Block randomization was used. Stratification was carried out according to the center. With the help of SAS 9.4 statistical software, the random number table of central coding was generated for a given number of seeds. The subjects were randomly divided into *Liang-Xue-Di-Huang* Decoction with the addition of Diosmine mimetic agent, or Diosmine with the addition of *Liang-Xue-Di-Huang* Decoction mimetic agent. An independent person (Zhao-feng Shen), who is not involved in observation or assessment of the patients possesses the computer-generated randomization sequence.

The randomization procedure will be conducted by research assistants using an online computerized randomization system (https://sci.medroad.cn/).

Blinding

This trial is a double-blind trial, divided into the *Liang-Xue-Di-Huang* Decoction with the addition of Diosmine mimetic agent, or Diosmine with the addition of *Liang-Xue-Di-Huang* Decoction mimetic agent. The double levels of blinding are sealed separately. Treatments are blinded to the patients and investigators (including statisticians) until the entire study is completed. Each hospital receives an emergency letter, along with these test drugs, properly preserved until the end of the trial.

Code-breaking should occur only in the case of serious adverse events happen or further intervention of the patient needs to know the actual medication situation, with the permission of the person in charge of the research center, and a report should be submitted to the leader of the trial within 24 hours

Eligibility criteria

Inclusion criteria:

1.Comply with hemorrhoids standards diagnosis (stage I, □, □)[2];

2.Comply with "Traditional Chinese Medicine Disease and Syndrome, Diagnosis and Curative Effect Standard" damp-heat syndrome:bleeding hemorrhoids, bright red blood[11];

3.Patient signed the informed consent form;

4. Patient agreed to avoid taking study agents outside the trial;

Exclusion criteria:

1.Patient had accompanied by severe liver, kidney, heart, brain, or lung dysfunction;

2.Patient had a history of inflammatory bowel disease, or a history of colorectal cancer, or had a history of any cancer;

4.Patient had a perianal abscess, anal fistula, rectal polyp, intestinal tumor or intestinal infectious disease;

5.Patient will plan pregnancy during this study;

6.Patient is pregnant or lactating women at the time;

7.Patient was allergic to test drugs and their ingredients;

8.Patient had unability to understand the nature of the study and follow the doctor’s recommendations.

9. Patient purchase or take other hemorrhoids medicine during this study period.

10. Patient had a history of bleeding disorders other than HD.

Test drugs

Test drugs include *Liang-Xue-Di-Huang* Decoction, *Liang-Xue-Di-Huang* Decoction mimetic agent, Diosmine and Diosmine mimetic agent. *Liang-Xue-Di-Huang* Decoction mimetic agent was consisted of 5 *Liang-Xue-Di-Huang* Decoction materials, as well as maltodextrin, food coloring, and bitters. *Liang-Xue-Di-Huang* Decoction and *Liang-Xue-Di-Huang* Decoction mimetic agent are provided by Tianjiang Pharmaceutical Group Co. Ltd, Wuxi, China. Diosmine mimetic agent was consisted of 5 Diosmine materials, as well as maltodextrin, and food coloring. Diosmine and Diosmine mimetic agent are provided by NANJING CHIA TAI TIANQING Group Co. Ltd, Nanjing, China. All these mimetic agents have the same shape, size, taste, colour, package and Lot number.

Interventions

Liang-Xue-Di-Huang Decoction with the addition of Diosmine mimetic agent

Patients will take one *Liang-Xue-Di-Huang* Decoction per day, 2 times a day, be took 1 hour after lunch and dinner meals. Diosmine mimetic agent, 0.45g each time, 2 times a day, be took 2 hours after lunch and dinner meals. The course of treatment will last 7 days, unless there is a loss of follow-up. Patients will be contacted by telephone in 7 and 14 days, and queried regarding adherence to study agents, illnesses, medication and supplement use. The assessment that needs to be performed at visit are listed in Figure 2.

Diosmine with the addition of *Liang-Xue-Di-Huang* Decoction mimetic agent

Diosmine with the addition of *Liang-Xue-Di-Huang* Decoction mimetic agent group's treatments and measurements will be in accordance with *Liang-Xue-Di-Huang* Decoction with the addition of Diosmine mimetic agent group.

Outcome measures

According to the latest treatment guidelines for HD[2], the primary outcome measure of this study is the French Bleeding Score (Table 2) in 7 and 14 days. The Secondary outcome measure are Goligher

Prolapse Score (Table 3) and Quality-of-Life Score (Table 4) in 7 and 14 days[available online at *www.jvir.org*].

Emergency symptomatic treatment (serious bleeding)

If patients have the following problems during this trial, such as a large amount of ejection bleeding accompanied by a significant decrease in hemoglobin, increased heart rate, and decreased blood pressure, patients will be discontinued and hospitalized.

Adverse events

All adverse events, including toxicity and side effects, such as gastrointestinal reaction, liver damage, and renal failure will be recorded and graded in detail throughout the study. When a severe adverse event occurs, researchers will provide every necessary treatment, and report the adverse event to the ethic committee of Affiliated Hospital of Nanjing University of Chinese Medicine.

Safety evaluation

A blood routine examination, routine urine test, liver function test, renal function test, electrocardiograph, and urine pregnancy test (women only) will be administered for safety outcomes, which are monitored both before and after clinical intervention.

Data management

Information from the clinical examination, as well as evaluation of treatment efficacy, will be recorded in each patient’s case report form (CRF). The study record is the source document of clinical study subject and should be kept in group leader's hospital. Each center will design designated personnel to be the electronic CRF input staff. Upon completion of each subject observation, the investigator will promptly submit the study record to the CRF inputter. The electronic CRF encoder must review whether the project record of the study notes is complete and report on time.

Data monitoring committee

This clinical data monitoring committee was composed by Affiliated Hospital of Nanjing University of Chinese Medicine and Jiangsu Famous Medical Technology Co., Ltd, Nanjing, China.

Patient's privacy protection

Only researchers and arbitrator who will sign the confidentiality commitment in this clinical trial may come into contact with the participants' personal health records. Drug regulatory departments have the right to inspect the records of clinical trials. Data will be processed anonymously, and information identifying individual subjects will be omitted. Patient's medical records will be stored in group leader's data archives

Statistical analysis

Frequency, median, and mean±standard deviation of the bleeding score, goligher prolapse score and quality-of-life score will be used for descriptive statistics. The statistical analysis will be performed using SAS 9.4. P<0.05 is considered statistically significant.

Discussion

HD is a well-defined clinical and pathophysiological placement between benign conditions but with high impact on quality of life[12]. Bleeding is the main symptom of HD[4]. It is estimated that 50% of people over 50 years of age have experienced symptoms of HD at least once in their life, and one-third of patients affected by HD seek medical attention[13,14]. Excessive bleeding can lead to an emergency situation. Hemorrhoidectomy and stapled hemorrhoidopexy are validated and effective surgical techniques, but are associated with long, painful postoperative courses.[15]. Contrary to common belief, a nonsurgical treatment is quite effective to manage HD[16], which can be offered with expectations of minimal harm[6]. Therefore medical therapy should be the first-line therapy for this disease[17].

Liang-Xue-Di-Huang Decoction has been used to treat HD from the 19th century in China and rich experience has been accumulated. In 2018, National Administration of Traditional Chinese Medicine of People's Republic of China published 100 classic prescriptions of ancient Chinese medicine, which contained *Liang-Xue-Di-Huang* Decoction[9]. These classic prescriptions of ancient Chinese medicine can be directly used in clinical treatment in China. In this classic *Liang-Xue-Di-Huang* Decoction, *Sophora japonica L.* (Huaijiao) and *Platycladus orientalis(L.)Franco* (Cebaiye) are the Jun (emperor) components. *Sophora japonica L.* (Huaijiao), which was first recorded in Sheng Nong's herbal classic, was commonly applied in clinical practice for the treatment of hematochezia from the 1th century in China. It has the effect of cooling blood, stopping bleeding, clearing heat in bowels and eliminating swell and easing pain[18]. Modern pharmacological studies have demonstrated its efficacy for stopping bleeding and anti-inflammation[19]. *Platycladus orientalis(L.)Franco* (Cebaiye) is categorized as a bloodcooling and hematostatic herb, which is usually prescribed with heat-clearing herbs to reinforce the efficacy of hemostasis. *Sanguisorba officinalis L.* (Diyu), *Coptis chinensis Franch*. (Huanglian), *Rehmannia glutinosa Libosch.* (Shengdihuang) are the Chen (minister) components, synergize with Jun to strengthen its therapeutic effects. In traditional Chinese medicine (TCM), *Sanguisorba officinalis L.* (Diyu) is often mixed with other herbs for the treatment of bleeding hemorrhoids. *Coptis chinensis Franch*. (Huanglian) has the effect of detumescence, clinically used for the treatment of hemorrhoid. *Rehmannia glutinosa Libosch.* (Shengdihuang) has been traditionally used as a blood cooling hemostatic. The Zuo (assistant) components, *Angelica sinensis(oliv) Diels.* (Danggui), *Citrus aurantium L.* (Zhike), *Scutellaria baicalensis Georgi.* (Huangqin), *Paeonia lactiflora Pall.* (Chishao), *Schizonepeta tenuifolin Briq.* (Jingjie), and *Trichosanthes Kirilowii Maxim* (Tianhuafeng), activate blood circulation to remove stasis, eliminate possible adverse effects of the Jun and/or Chen components. The Shi (courier) components, *Cimicifuga heraclei folia.Kom* (Shengma), and *Glycyrrhiza uralensis Fisch.* (Shenggancao) facilitate the overall

action of the other components. Theoretically, *Liang-Xue-Di-Huang* Decoction work through the TCM therapeutic principle“Jun-Chen-Zuo-Shi”, to relieve bleeding hemorrhoids and diminish hemorrhoids prolapsed.

Although TCM has been clinically practised for thousands of years, most Chinese herbal medicine products do not possess up-to-date regarding about their safety and modern scientific evidences for their claimed clinical uses. TCM safety research is becoming more standardized and is gradually aligning with international standards. A randomized, controlled, blind, and multicenter trial will be helpful for further prove the efficacy and safety of *Liang-Xue-Di-Huang* Decoction as an treatment for HD.

Abbreviation

Hemorrhoidal disease	HD
Case report form	CRF
Traditional Chinese medicine	TCM

Declaration

Trial status

The protocol version number is NO.2 and the date is January 10, 2019. At the time of manuscript submission, patient's recruitment for the trial is on-going. The clinical study will begin from Aug, 2019 and end in Dec, 2020. A total of 240 Chinese patients will be recruited in this clinical study.

Funding

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Authors’ contributions

Qing Zhou and Shuo-yang Shi contributed to the design of the study protocol. Tuo Chen participated in the statistical design and helped in the design of the study. Ben-sheng Wu, Cheng-biao Xu, Ji Geng, Dan Zhang, Feng Jiang and Zhong-qi He helped to draft the manuscript and participated in the project development. Yu-Gen Chen was the project leader for this research and participated in the critical revision of the manuscript. All authors have read and approved the final manuscript.

Competing interests

None.

Acknowledgements

Not applicable.

Consent for publication

Individual participant image or other clinical detail is not applicable.

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Tables

Table 1 Standard formulation of *Liang-Xue-Di-Huang* Decoction

Pinyin name	Latin name	Doses	Pinyin name	Latin name	Doses
Huaijiao	*Sophora japonica L.*	9g	*Cebaiye*	*Platycladus orientalis(L.)Franco*	6g
Diyu	*Sanguisorba officinalis L.*	6g	*Huanglian*	*Coptis chinensis Franch.*	6g
Shengdihuang	*Rehmannia glutinosa Libosch.*	*6g*	*Danggui*	*Angelica sinensis(oliv) Diels.*	4.5g
Zhike	*Citrus aurantium L.*	3g	*Huangqin*	*Scutellaria baicalensis Georgi.*	3g
Chishao	*Paeonia lactiflora Pall.*	3g	*Jingjie*	*Schizonepeta tenuifolin Briq.*	3g
Tianhuafeng	*Trichosanthes Kirilowii Maxim.*	2.4g	*Shengma*	*Cimicifuga heraclei folia.Kom*	1.5g
Shenggancao	*Glycyrrhiza uralensis Fisch.*	1.5g			

Table 2 French Bleeding Score (Possible Score=0-9)	
Frequency	
Never	0
>1 per year	1
>1 per month	2
>1 per week	3
>1 per day or bowel movement	4
Bleeding	
Never	0
At wiping	1
In the toilet	2
On underwear	3
Anemia	
Never	0
Without transfusion	1
With transfusion	2

Table 3 Goligher Prolapse Score (Possible Score=0-3)		
Grade 1	No protrusion	0
Grade 2	Protrusion with spontaneous reduction	1
Grade 3	Protrusion requiring manual reduction	2
Grade 4	Protrusion that cannot be reduced	3

Table 4 Quality-of-Life Score (Possible Score=0-4)	
No discomfort	0
Mild discomfort	1
Moderate discomfort	2
Significant discomfort	3
Permanent discomfort	4

Figures

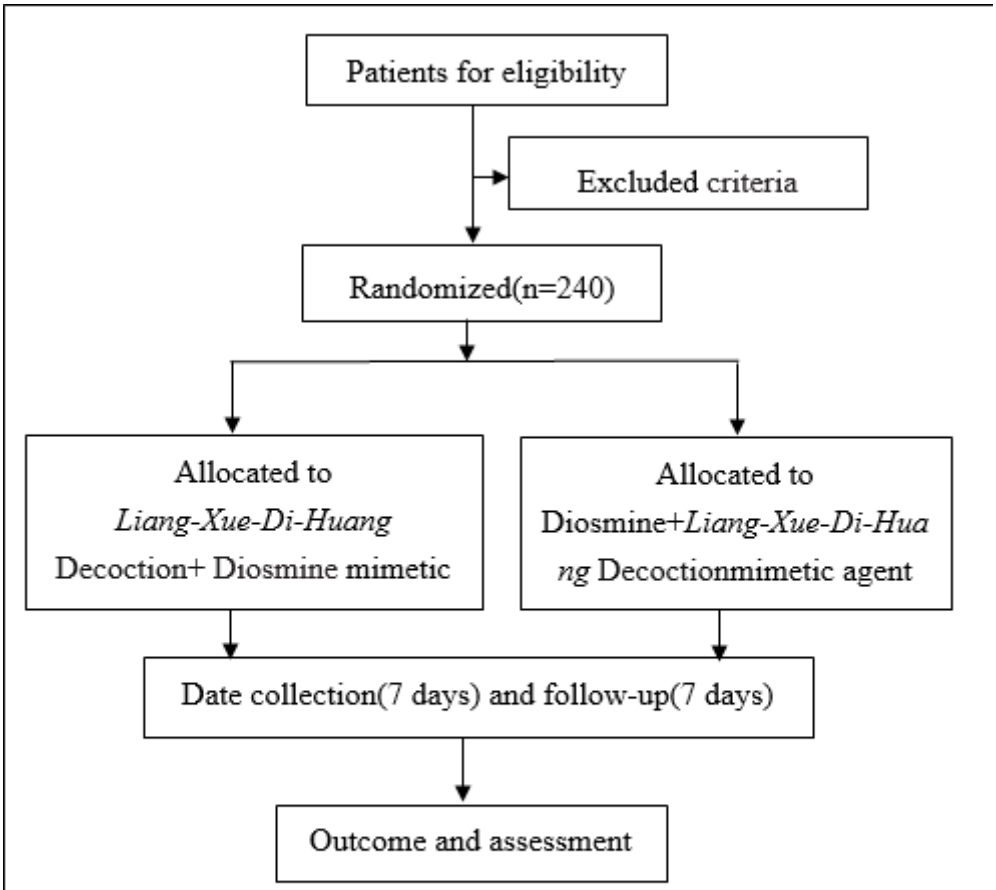
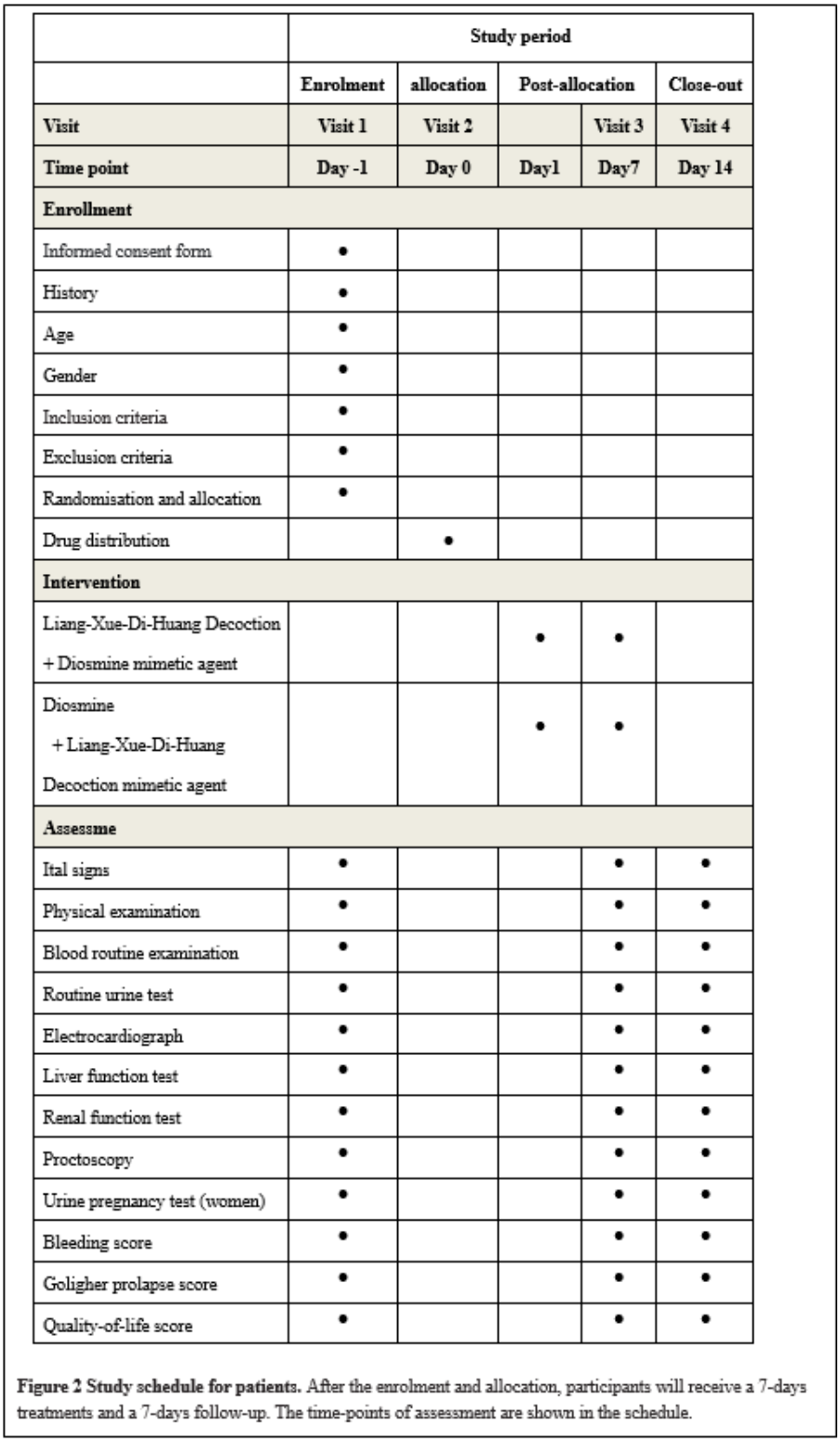


Figure 1 Study flow chart. The flow chart of enrolment,allocation,intervention and assessment.

Figure 1

Study flow chart. The flow chart of enrolment, allocation, intervention and assessment.



	Study period				
	Enrolment	allocation	Post-allocation		Close-out
Visit	Visit 1	Visit 2		Visit 3	Visit 4
Time point	Day -1	Day 0	Day1	Day7	Day 14
Enrollment					
Informed consent form	•				
History	•				
Age	•				
Gender	•				
Inclusion criteria	•				
Exclusion criteria	•				
Randomisation and allocation	•				
Drug distribution		•			
Intervention					
Liang-Xue-Di-Huang Decoction + Diosmine mimetic agent			•	•	
Diosmine + Liang-Xue-Di-Huang Decoction mimetic agent			•	•	
Assessme					
Ital signs	•			•	•
Physical examination	•			•	•
Blood routine examination	•			•	•
Routine urine test	•			•	•
Electrocardiograph	•			•	•
Liver function test	•			•	•
Renal function test	•			•	•
Proctoscopy	•			•	•
Urine pregnancy test (women)	•			•	•
Bleeding score	•			•	•
Goligher prolapse score	•			•	•
Quality-of-life score	•			•	•

Figure 2 Study schedule for patients. After the enrolment and allocation, participants will receive a 7-days treatments and a 7-days follow-up. The time-points of assessment are shown in the schedule.

Figure 2

Study schedule for patients. After the enrolment and allocation, participants will receive a 7-days treatment and a 7-days follow-up. The time-points of assessment are shown in the schedule.

Supplementary Files

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- Formula1.jpg
- 20191229SPIRITChecklist.docx