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TITLE PAGE

Title:

Hepatic venous pressure gradient guided laparoscopic versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

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ABSTRACT

Introduction

Gastroesophageal variceal bleeding is one of the most common and severe complications with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous pressure gradient (HVPG) is a globally recommended golden standard for portal pressure assessment and an HVPG ≥ 16mmHg indicates a higher risk of death and rebleeding. This study aims to compare the effectiveness and safety of laparoscopic therapy plus propranolol and endoscopic therapy plus propranolol for variceal rebleeding in cirrhotic patients with HVPG between 16 and 20 mmHg.

Methods and analysis

This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding will be recruited from three sites in China. Participants will receive either endoscopic therapy plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous thrombosis, quality of life and tolerability of treatment. Outcome measures will be evaluated at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks. Multivariate COX regression model will be introduced for analyses of occurrence data and Kaplan-Meier analysis with Log-rank Test for inter-group comparison. Student's t test, Wilcoxon rank sum test, chi-squared test or Fisher's exact test will be applied for analyses of other outcomes.

Ethics and dissemination

Ethical approval was obtained from all three participating sites. Primary and secondary outcome data will be submitted for publication in peer-reviewed journals and widely disseminated.

Trial registration number

NCT03783065; Pre-results.

Trial status

Recruitment for this study started on December 2018 while the first participant was randomized on January 2019. Recruitment is estimated to stop on October 2019.

Strengths and limitations of this study

- This study is the first trial that concentrates on the best management on prevention of rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.
- This trial is the first one to compare the effectiveness of laparoscopic therapy plus propranolol to endoscopic therapy plus propranolol recommended by international guidelines.
- The surgical procedure involved in this study employs minimally invasive laparoscopy instead of conventional operation, minimizing trauma and complications.
- Limitations of this trial include the lack of accessible data for sample size estimation, potential influence in applicability in other countries due to etiological differences and the relatively short follow-up period.

INTRODUCTION

Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.[1] Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients and those who developed variceal bleeding face a mortality of 5-20%.[2 3] Thus, the stratification and applicable secondary prevention for patients with high risk is of great clinical significance.

Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure and free hepatic venous pressure.[4] Eliminating the influence of abdominal pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has been demonstrated to have good performances in risk stratification [3 5] and predicting the

response to treatments.[6 7] An HVPG over 12 mmHg suggests the occurrence of gastroesophageal variceal bleeding.[8] Patients with HVPG over 16mmHg face higher risk of death [8-11] and rebleeding,[6] while an HVPG over 20 mmHg predicts failure to control bleeding, early rebleeding, and death due to acute variceal hemorrhage.[12 13] Currently, international guidelines recommend endoscopic therapy combined with non-selective beta-blockers to be the first-line therapy of secondary prevention for cirrhotic patients with gastroesophageal variceal bleeding.[3 5] Nevertheless, patients with high HVPG still suffer from risk of treatment failure. Recent years, early TIPS is recommended as a better choice for patients with HVPG ≥ 20 mmHg,[14 15] while there still lack a strong evidence to determine the best method for patients with HVPG between 16 and 20 mmHg.

Splenectomy and pericardial devascularisation, first performed by Hassab,[16 17] is a promising surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the first laparoscopic splenectomy was reported in 1991,[18] post-operational complications which used to be a major concern of Hassab's operation have been cut down to a great extent due to less invasive procedures.[19] Laparoscopic therapy has been widely accepted for variceal bleeding in Asia-pacific countries, where the predominant etiology of cirrhosis is hepatitis B virus infection[20] combined with very high occurrence of hypersplenism.[21] However, there haven't been any prospective trials comparing the effectiveness of laparoscopic therapy plus propranolol to the internationally recommended first-line therapy. Also, the precise indication to perform laparoscopic therapy is still unclear.

In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg will be compared to explore the optimized management. Taking into consideration the preferred performance of HVPG in risk stratification and the lack of prospective study in long-term performance of laparoscopic therapy, this trial will be meaningful for both the extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.

Objectives

The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose

transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding compared with endoscopic therapy plus propranolol. The primary outcome will be variceal rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, quality of life and tolerability of treatment. We hypothesise that:

1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is more effective in reducing variceal rebleeding.

2. Participants receiving laparoscopic splenectomy and pericardial devascularisation plus propranolol show non-inferior overall survival and lower occurrence of hepatocellular carcinoma over those who receiving endoscopic therapy plus propranolol.

3. The occurrence of venous thrombosis, QOL and KPS scores are without significant difference between two groups.

METHODS AND ANALYSIS

Study design

This study is a multicenter, prospective, randomized controlled clinical trial. The overview of the study process is illustrated in Figure 1. After screened for eligibility, the participants will be randomly allocated to laparoscopic group or endoscopic group. After the operative intervention, there will be a 60-week follow-up period. All tests and interventions will be performed at three involved centers in China: (1) Shunde Hospital, Southern Medical University, (2) Xingtai People's Hospital and (3) The First Hospital of Lanzhou University.

Eligibility criteria

Inclusion criteria

Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving endoscopic treatment, (d) screened with transjugular HVPG between 16 and 20 mmHg after hospitalization, (e) with ECOG score ≤ 2 and KPS score ≥ 60 during screening, (f) assessed to be Child-Pugh class A or B and (g) voluntarily participate in the study and able to provide written informed consent and able to understand and willing to comply with the requirements

of the study.

Exclusion criteria

Those who conforms to any of the following would be excluded: (a) pregnant or breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick < 50%, PTT > 50 sec, thrombocyte count < 50000 / µl or disturbed thrombocyte function), (d) with massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for transjugular HVPG measurement and (g) with other situations whose existence judged inadequate for participation by the investigators.

Recruitment

Recruitment has started in December 2018 and will continue until the intent sample size has been reached. Participants (n = 40) from China are recruited in three sites through (1) posters, which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the advice of the doctors.

Patient and public involvement

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

Randomisation

Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the endoscopic group after signing on an informed consent, before which the patients will be informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (≤ 60 years or ＞ 60 years) and gender. For the randomization, the randPack package of R software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The randomisation will be generated by a statistician independent of the study.

Operative interventions

All operative interventions will be performed by trained and experienced specialists affiliated

to the university centers. Doppler ultrasonography, CT, electrocardiogram and esophagogastroduodenoscopy will be performed routinely pre-operation.

Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h after randomisation. Laparoscopic therapy will be performed as previously described.[20] General anesthesia will be applied for all participants. Major procedures of the operation include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of abdominal esophagus from the stomach coronary vein. During the process of devascularisation, the high esophageal branches and heterotopic high esophageal branches will be carefully screened.

Participants assigned to the endoscopic group will undergo initial endoscopic therapy within 48h after randomisation. Candidate procedures for endoscopic therapy include endoscopic variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which procedure to adopt will be made by experienced specialist according to the condition of the participant, while EVL will be considered the first option as recommended by guidelines.[3 5] Treatments will be performed again every 1-2 week until completely eradication of varices.

Propranolol oral administration

Participants assigned to both groups will begin to receive propranolol after the randomisation. Propranolol shall be administrated orally while keeping monitoring the heart rate and blood pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days (maximum dose: 320 mg/d for participants without ascites, 160 mg/d for participants with ascites) to achieve a resting heart rate of 55-60 beats/min while the systolic blood pressure maintain > 90 mmHg.[5] The dose can always be adjusted according to the response on participants.

Outcomes and assessments

Primary outcome

In order to compare the effectiveness of laparoscopic group with endoscopic group, the

primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year rebleeding rate and rebleeding time.

Secondary outcomes

Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, quality of life and tolerability of treatment. Following endpoints will be applied, respectively: (1) overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the occurrence of venous thrombosis, (4) quality of life (QOL) score and (5) Karnofsky (KPS) score. QOL score and KPS score are treated as the reflection of safety and tolerability of treatment. The occurrence and exact kind of adverse events will be recorded to this end and treated as an outcome candidate. Also, serum markers will be introduced for monitor of change on liver functions and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
Quality of life			x	x	x	x	x
Karnofsky			x	x	x	x	x

Assessments

Time points of involved assessments to be performed are outlined in Table 1. For participants allocated to either the groups, the following assessments will be performed and corresponding data will be collected:

1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
2. Disease history with clear record about the number of occurrence of gastroesophageal variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis,

hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal syndrome and hepatopulmonary syndrome, etc.

3. Clinical diagnosis and etiology for cirrhosis.

4. Laboratory test results including red blood cells, white blood cells, haemoglobin, blood ammonia, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum creatinine.

5. Color Doppler ultrasound results including general condition of spleen and liver, spleen diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous reflux, cardiac output, left ventricular ejection fraction and heart output.

6. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.

7. Abdominal CT scans.

8. Esophagogastroduodenoscopy results including the location, classification, diameter of varices and red signs.

9. Electrocardiogram results.

10. Child-Pugh score and classes.

11. QOL score.

12. KPS score.

13. Adjustment records of dosage of propranolol.

14. Adverse events and severe adverse events of any cause.

Upon occurrence of the first variceal rebleeding after the operative intervention, the following data will be additionally collected:

1. Cause of rebleeding.

2. Time of rebleeding since enrollment.

3. Treatment and outcome of the rebleeding.

Upon death of a participant, the following data will be additionally collected:

1. Time of death since enrollment.

2. Cause of death.

Sample size estimation

No study has yet compared the outcome between cirrhotic patients with gastroesophageal variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy plus propranolol oral administration, the sample size is determined based on pooled data of variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy plus propranolol oral administration is estimated by 6 RCTs (Table 2).[22-27] The variceal rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).[20] [28-32] Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44% and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate (1-β) of 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

Ethics and dissemination

Ethical approval was obtained from all three participating centers. Any modifications in protocol will be done under the premise of adequate communication and approval. All interventions and assessments included in this trial will be in full compliance with Good Clinical Practice (GCP).

Before the allocation, all participant candidates will be fully informed about the purpose, process and possible consequences of the trial. Before any treatment, the participants will be

informed about the interventions they will undergo and the interventions will not be applied before a written informed consent signed by the participants themselves is provided.

The result of this trial (CHESS1803) will be presented at national and international conferences and published in peer-reviewed journals.

Safety

Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic therapy is generally implemented worldwide. Both surgical interventions showed low risks of severe adverse events. Nevertheless, the participants and whose relatives will be able to contact the study team when any severe adverse event or disease complication occurs. The participants will receive proper treatments as soon as feasible.

The following data will be recorded when an adverse event occurs:

1. The exact kind of adverse event.
2. The starting, ending and reporting time of the adverse event.
3. Severity of the adverse event.
4. Treatment and outcome of the adverse event.

Adverse events will be documented and reported to the investigators and ethics board of the involved center in 48h. Severe adverse events will be documented and reported to the investigators and ethics board of the involved center, principle investigator and supervision departments required by GCP immediately.

Data management

For imaging data, the electronic form images will be collected. Other raw data will be recorded in the written form case report form first and saved electronically afterwards. All electronic data will be kept by a member of the study team without direct clinical contact with any of the centers. All written form data will be stored in cabinets with lock permitting access for only investigators. All data will be kept for 25 years after publication and destroyed after then.

Statistical analyses

Statistical analyses will be performed in intention-to-treat cases. No interim analyses will be conducted on the primary outcome. Multivariate COX regression model will be introduced for analyses of variceal rebleeding and survival, while applying Kaplan-Meier analysis with Log-rank test for inter-group comparison. Occurrence data including variceal rebleeding, overall survival, hepatocellular carcinoma and portal venous thrombosis will be compared using the chi square test. For data with repeated measurements including QOL score, KPS score and laboratory tests results, repeated measures ANOVA will be applied. The occurrence and severity of all adverse events will be collected and compared with descriptive analyses and Wilcoxon rank sum test. Student's t test or Wilcoxon rank sum test (for continuous data) and chi square test or Fisher's exact test (for discrete variable) will be applied for analyses of other unmentioned outcomes. All results will be presented with 95% CIs.

DISCUSSION

To the best of our knowledge, this study is the first to compare the effectiveness and safety of laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line therapy recommended by international guidelines,[3 5] under an HVPG-guided manner. The risk stratification performance of HVPG has been receiving more concentration and several attempts have been made on HVPG-guided therapy.[33 34] By introducing HVPG restriction as an eligibility criterion, this study targets the population that faces high risk of variceal rebleeding and death[6 8-11] better, enabling exploration of better management for these patients as well as extension of clinical performance of HVPG.

The first splenectomy and pericardial devascularisation was performed by Hassab in 1964[35] and modified by Qiu Fazu in 1981.[36] Benefitted from the rapid development of laparoscopic equipment and techniques, surgical procedures for variceal bleeding are becoming decreasingly invasive and also with much lower occurrence of adverse events.[20 29 37-39] Such laparoscopic therapy has been accepted as one of the most common used methods for variceal bleeding in Asia-pacific countries. Pericardial devascularisation and splenectomy increase the blood flow of portal vein and ameliorate leukopenia and thrombocytopenia. Thus, laparoscopic therapy is considered an effective method for variceal bleeding while only

minimally affect liver function with satisfying performance on long-term survival and general condition of patients. However, it is also reported to be correlated with high occurrence of portal venous thrombosis[40] and exacerbation of portal hypertensive gastropathy.[41] Therefore, a multicenter prospective study about laparoscopic therapy will provide valuable information for the clarification of its influence to the overall outcome.

Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy and widely served as control groups in many studies.[22-27 42] On the contrary, studies about laparoscopic therapy are mainly single-arm[20 32 43] or compared with variants and other surgeries.[28-31 40 44 45] To the best of our knowledge, there haven't been any trials about laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls. Thus, this study will also provide data with better comparability to other commonly used therapies.

Still, this study has several limitations. First, this is the first prospective study investigating the HVPG-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic therapy plus propranolol. The lack of enough previous studies may lead to deviations in sample size estimation. Second, the major cause of cirrhosis of the target population of this study is hepatitis B virus infection while it is more complex in American and European countries. Differences in etiology may bring problems in applicability. Third, the period of follow-up in this study is set to be about one year, which may not be enough to thoroughly unfold the long-term effect of laparoscopic therapy.

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Contributors Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang and Chuan Liu are responsible of the data collecting and management. Ruoyang Shao drafted this manuscript. Ruizhao Qi, Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version of the manuscript was reviewed and approved by all authors.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study has been approved by the ethics committee of Shunde Hospital, Southern Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou University (LDYYLL2019-179).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data from this study will be made available upon reasonable request. To request for data, please contact the corresponding author.

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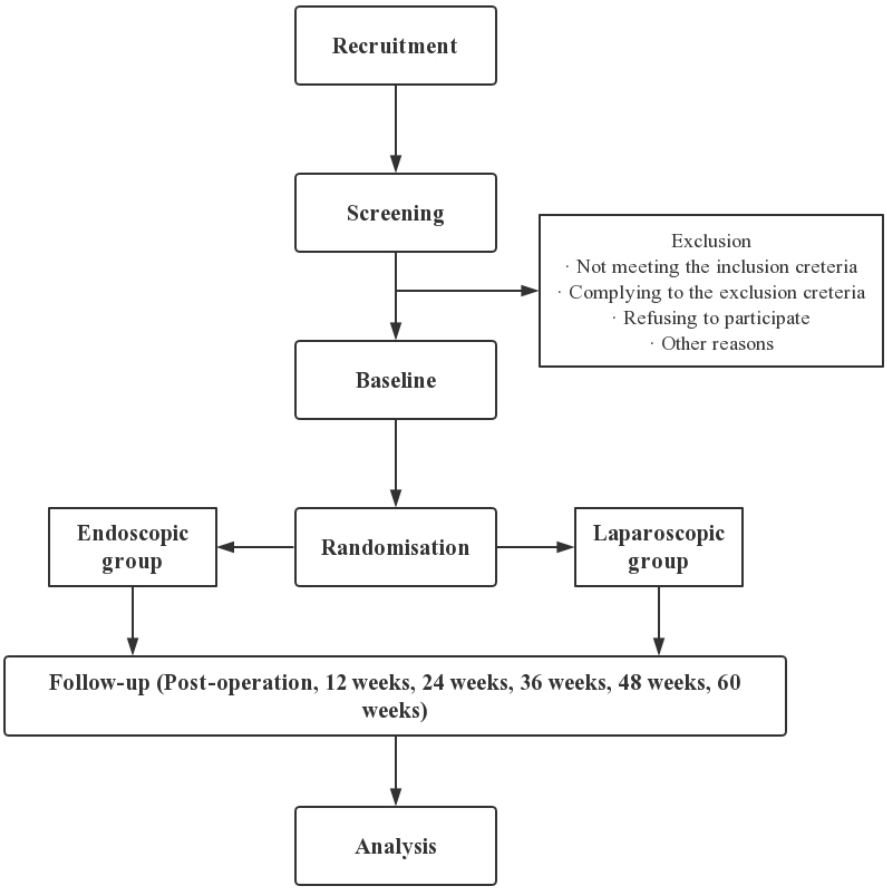

Flow chart for study design.

Informed Consent Form

Dear madam/sir,

You are invited to participate in a multicenter randomized controlled trial assessing the effectiveness and safety of laparoscopic therapy plus propranolol as first-line therapy of secondary prevention for cirrhotic patients with gastroesophageal varices. The following items contain important information including the background, aim, method, possible merits and risks for participants about this trial. We would like to request you to read them carefully before you make your decision for they may assist you to decide whether to participate in this trial or not. If you have any questions, please contact the investigator in charge for this trial directly to ensure your fully understanding. Your participation is of completely voluntary. Please sign in the statements section of this form if you agree to participate.

Aim of study

Laparoscopic therapy is one of the most commonly used interventions for gastroesophageal variceal bleeding. Current experience in clinical practice has proved it to be a promising procedure to control rebleeding bringing only minimal trauma and bleeding. In this trial, we intend to compare laparoscopic therapy plus propranolol to endoscopic therapy plus propranolol, the first-line therapy currently recommended by international guidelines, to evaluate the effectiveness and safety of laparoscopic therapy for secondary prevention of cirrhotic patients with history of gastroesophageal variceal bleeding.

Design and interventions

This is a prospective, multicenter randomized controlled trial. 40 participants will be recruited in this trial.

Appropriate participants will be invited by the investigators according to the inclusion

and exclusion criteria and randomly assigned to the endoscopic group or the laparoscopic group. Participants in the endoscopic group will receive endoscopic therapy plus propranolol and those in the laparoscopic group will receive laparoscopic therapy plus propranolol. For participants assigned to the endoscopic group, either of the procedures including endoscopic variceal ligation, cyanoacrylate glue injection and sclerotherapy. Decision of which procedure to be adopt for each participant will be individually made by experienced specialist according to the condition of the varices. Nevertheless, EVL will be considered the first option when there are multiple appropriate procedures as recommended by international guidelines.

Term and procedure

During the trial, the staff will perform corresponding procedure for the participants according to the assignation after necessary tests and data collection been performed. Propranolol administration will start since assignation. The term of the trial for each participant will be 60 weeks. Follow-up will take place on week 12, 24, 36,48 and 60 since enrollment. The following data will be collected during the procedure:

- General information: gender, date of birth, height, weight, ethnic.
- Clinical data: type of portal hypertension, etiology for cirrhosis, co-morbidity, combined medication, time of bleeding.
- Test results: blood routine, blood coagulation, liver function, esophagogastroduodenoscopy, renal function, Color Doppler ultrasound, abdominal CT, electrocardiogram, transient elastography, QOL score, KPS score, etc.
- Adjustment records of dosage of propranolol, adverse events and severe adverse events.

Possible conflict of interest

The trial has no possible conflict of interest with participants.

Possible merits

All participants will receive either endoscopic therapy or laparoscopic therapy, plus propranolol oral administration. Either therapy is widely performed and accepted and may lower rebleeding rate and improve survival and life of quality. Furthermore, all clinical events the participants will be carefully monitored and managed by the staff.

Possible risks

Possible risks include complications of endoscopic therapy (including but not limited to nausea, vomit, fervescence, esophagostenosis, esophageal ulcer, dysphagia and early rebleeding), laparoscopic therapy (including but not limited to intraoperative hemorrhage, portal vein thrombosis, subphrenic infection, pancreatic fistula and early rebleeding) and side-effects of propranolol. All clinical events will be carefully monitored and managed by the staff in order to minimize possible risks.

Upon occurrence of safety issues during the process, the trial will be terminated, and necessary medical procedures will be performed for participants suffering from research related adverse effect. If the reason is confirmed to be non-human factors, the trial will be announced failure.

Confidentiality

The individual privacy of participants will be carefully preserved during the trial. The Food and Drug Administration and Ethics Committee have the right to censor the materials related to the participants when necessary. Any private information of participants will not be disclosed upon publication of the result of this study.

Voluntarity

The participation and exit of this study is of completely voluntary. Participants have the right to exit the study at any time without getting penalized, discriminated or retaliated of any form. Nevertheless, the research group strongly recommend all participants to cooperate and complete the process.

The process of a participant may be terminated by the investigator if the participant requests other diagnosis or treatment, failed to comply to the plan or for any other reasonable cause.

Ethics approval

This study has been reported to the ethics committee of XXX hospital and been approved after thorough investigation on ethical issues. Please contact the ethics committee upon any ethical concerns.

If you have read and fully understood the above items and agree to participate, please sign the statements below.

Statements

Statement of participant

I have carefully read and understood the contents of this informed consent form. I have the chance to question to the investigators and all questions have been answered. I understand that my participation is of completely voluntary. I agree that related medical data to be used for research and publication. I understand that I have the right to exit the study at any time without getting penalized, discriminated or retaliated, in which case my subsequent medical treatment will not be affected.

If I request other diagnosis or treatment, failed to comply to the plan or for any other reasonable cause, the investigators have the right to terminate my participation. I volunteer to participate in this trial and I will receive a copy of signed informed consent form.

Participant: _____

Data: _____ Time: _____:_____

The legal guardian of the participant or an impartial witness should sign in the case of incapability of the participant to sign for any reason.

Legal guardian/impartial witness: _____

Relationship with the participant: _____

Data: _____ Time: _____:_____

Statement of investigator

I have accurately informed the participant about this informed consent form and responded to all questions asked. The participant volunteer to participate in this trial.

Investigator: _____

Data: _____ Time: _____:_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 65)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 15/line 386)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 14/line 369)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
(P 15/line 390)	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale (P 4/line 84)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives (P 5/line 123)	7	Specific objectives or hypotheses

Trial design (P 6/line 139)	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting (P 6/line 139)	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria (P 6/line 147)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions (P 7/line 184)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes (P 8/line 213)	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline (P 9/line 228)	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size (P 11/line 267)	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment (P 7/line 167)	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation: (P 7/line 176)		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods (P 9/line 230)	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management (P 12/ line 310)	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods (P 13/line 318)	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
(P13/line 319)	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms (P 12/line 294)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval (P 15/line 397)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments (P 11/line 281)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent (P 11/line 286)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality (P 12/line 309)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests (P 15/line 392)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data (P 12/line 309)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care (P12/line 293)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy (P 11/line 281)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials (supplementary file)	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology, Surgery, Research methods

Keywords:	Hepatology < INTERNAL MEDICINE, Hepatobiliary surgery < SURGERY, Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY

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TITLE PAGE

Title:

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial

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Hepatic venous pressure gradient, variceal rebleeding, randomized controlled trial

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3205 words

ABSTRACT

Introduction

Gastroesophageal variceal bleeding is one of the most common and severe complications with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous pressure gradient (HVPG) is a globally recommended golden standard for portal pressure assessment and an HVPG ≥ 16mmHg indicates a higher risk of death and rebleeding. This study aims to compare the effectiveness and safety of splenectomy and pericardial devascularization (laparoscopic therapy) plus propranolol and endoscopic therapy plus propranolol for variceal rebleeding in cirrhotic patients with HVPG between 16 and 20 mmHg.

Methods and analysis

This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding will be recruited from three sites in China. Participants will receive either endoscopic therapy plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous thrombosis, occurrence of adverse events, quality of life and tolerability of treatment. Outcome measures will be evaluated at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks. Multivariate COX regression model will be introduced for analyses of occurrence data and Kaplan-Meier analysis with Log-rank test for inter-group comparison.

Ethics and dissemination

Ethical approval was obtained from all three participating sites. Primary and secondary outcome data will be submitted for publication in peer-reviewed journals and widely disseminated.

Trial registration number

NCT03783065; Pre-results.

Trial status

Recruitment for this study started on December 2018 while the first participant was randomized on January 2019. Recruitment is estimated to stop on October 2019.

Strengths and limitations of this study

- This study is the first trial that concentrates on the best management on prevention of rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.
- This trial is the first one to compare the effectiveness of laparoscopic therapy plus propranolol to endoscopic therapy plus propranolol recommended by international guidelines.
- The surgical procedure involved in this study employs minimally invasive laparoscopy instead of conventional operation, minimizing trauma and complications.
- Limitations of this trial include the lack of accessible data for sample size estimation, potential influence in applicability in other countries due to etiological differences and the relatively short follow-up period.

INTRODUCTION

Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.[1] Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients and those who developed variceal bleeding face a mortality of 5-20%.[2 3] Thus, the stratification and applicable secondary prevention for patients with high risk is of great clinical significance.

Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure and free hepatic venous pressure.[4] Eliminating the influence of abdominal pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has been demonstrated to have good performances in risk stratification [3 5] and predicting the

response to treatments.[6 7] An HVPG over 12 mmHg suggests the occurrence of gastroesophageal variceal bleeding.[8] Patients with HVPG over 16mmHg face higher risk of death [8-11] and rebleeding,[6] while an HVPG over 20 mmHg predicts failure to control bleeding, early rebleeding, and death due to acute variceal hemorrhage.[12 13] Currently, international guidelines recommend endoscopic therapy combined with non-selective beta-blockers to be the first-line therapy of secondary prevention for cirrhotic patients with gastroesophageal variceal bleeding.[3 5] Nevertheless, patients with high HVPG still suffer from risk of treatment failure. Recent years, early transjugular intrahepatic portal-systemic shunts is recommended as a better choice for patients with HVPG $\geq$ 20 mmHg,[14 15] while there still lack a strong evidence to determine the best method for patients with HVPG between 16 and 20 mmHg.

Splenectomy and pericardial devascularization, first performed by Hassab,[16 17] is a promising surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the first laparoscopic splenectomy was reported in 1991,[18] post-operational complications which used to be a major concern of Hassab's operation have been cut down to a great extent due to less invasive procedures.[19] Laparoscopic splenectomy and pericardial devascularization (laparoscopic therapy) has been widely accepted for variceal bleeding in Asia-pacific countries, where the predominant etiology of cirrhosis is hepatitis B virus infection[20] combined with very high occurrence of hypersplenism.[21] However, there haven't been any prospective trials comparing the effectiveness of laparoscopic therapy plus propranolol to the internationally recommended first-line therapy. Also, the precise indication to perform laparoscopic therapy is still unclear.

In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg will be compared to explore the optimized management. Taking into consideration the preferred performance of HVPG in risk stratification and the lack of prospective study in long-term performance of laparoscopic therapy, this trial will be meaningful for both the extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.

Objectives

The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding compared with endoscopic therapy plus propranolol. The primary outcome will be variceal rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse events, quality of life and tolerability of treatment. We hypothesise that:

1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is more effective in reducing variceal rebleeding.
2. Participants receiving laparoscopic therapy plus propranolol show non-inferior overall survival and lower occurrence of hepatocellular carcinoma over those who receiving endoscopic therapy plus propranolol.
3. The occurrence of venous thrombosis and adverse events and QOL and KPS scores are without significant difference between two groups.

METHODS AND ANALYSIS

Study design

This study is a multicenter, prospective, randomized controlled clinical trial. The overview of the study process is illustrated in Figure 1. After screened for eligibility and measurement of HVPG, the participants will be randomly allocated to laparoscopic group or endoscopic group. After the operative intervention, there will be a 60-week follow-up period. All tests and interventions will be performed at three involved centers in China: (1) Shunde Hospital, Southern Medical University, (2) Xingtai People's Hospital and (3) The First Hospital of Lanzhou University.

Eligibility criteria

Inclusion criteria

Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving splenectomy or any secondary prevention, (d) screened with transjugular HVPG between 16

and 20 mmHg after hospitalization, (e) with Eastern Cooperative Oncology Group (ECOG) score ≤ 2 and Karnofsky performance status (KPS) score ≥ 60 during screening, (f) assessed to be Child-Pugh class A or B, and (g) voluntarily participate in the study and able to provide written informed consent and able to understand and willing to comply with the requirements of the study.

Exclusion criteria

Those who conforms to any of the following would be excluded: (a) pregnant or breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick < 50%, partial thromboplastin time (PTT) > 50 sec, platelet count < 50000 / μl or qualitative platelet dysfunction that affects conglutination function of congenital (Bernard-Soulier syndrome, Glanzmann thrombasthenia, storagepool disease, aspirin-like defects, platelet-type Von Willebrand disease, etc) or acquired (medication or other systemic diseases) causes), (d) with massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for transjugular HVPG measurement, (g) with active bleeding upon screening and (h) with other situations whose existence judged inadequate for participation by the investigators.

Recruitment

Recruitment has started in December 2018 and will continue until the intent sample size has been reached. Participants (n = 40) from China are recruited in three sites through (1) posters, which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the advice of the doctors.

Patient and public involvement

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

Randomization

Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the endoscopic group after signing on an informed consent, before which the patients will be

informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (≤ 60 years or ＞ 60 years) and gender. For the randomization, the randPack package of R software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The randomization will be generated by a statistician independent of the study.

HVPG measurement

Transjugular HVPG measurement will be performed for all participants when screening for eligibility by experienced interventional radiologists. The procedure will be performed using a balloon catheter with a pressure transducer at the tip (Edwards Lifesciences, Irvine, California). At first, a zero measurement will be made with the transducer open to air. After transjugular catheterization, free hepatic venous pressure will be measured in the right hepatic vein at about 1-3 cm from the inferior vena cava. Then, the right hepatic vein will be occluded completely by the inflated balloon, after which will the wedged hepatic venous pressure be measured. The measurement will be continued until the pressure reach a plateau. Measurements will be performed in at least triplicate, and the average value will be used. HVPG is the difference between wedged hepatic venous pressure and free hepatic venous pressure.

Operative interventions

All operative interventions will be performed by trained and experienced specialists affiliated to the university centers. Doppler ultrasonography, computed tomography (CT), electrocardiogram and esophagogastroduodenoscopy will be performed routinely pre-operation.

Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h after randomization. Laparoscopic therapy will be performed as previously described.[20] General anesthesia will be applied for all participants. Major procedures of the operation include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of abdominal esophagus from the stomach coronary vein. During the process of

devascularization, the high esophageal branches and heterotopic high esophageal branches will be carefully screened.

Participants assigned to the endoscopic group will undergo initial endoscopic therapy within 48h after randomization. Candidate procedures for endoscopic therapy include endoscopic variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which procedure to adopt will be made by experienced specialist according to the condition of the participant, while EVL will be considered the first option as recommended by guidelines.[3 5] Treatments will be performed again every 1-2 week until completely eradication of varices.

Propranolol oral administration

Participants assigned to both groups will begin to receive propranolol after the randomization. Propranolol shall be administrated orally while keeping monitoring the heart rate and blood pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days (maximum dose: 320 mg/d for participants without ascites, 160 mg/d for participants with ascites) to achieve a resting heart rate of 55-60 beats/min while the systolic blood pressure maintain > 90 mmHg.[5] The dose can always be adjusted according to the response on participants.

Outcomes and assessments

Primary outcome

In order to compare the effectiveness of laparoscopic group with endoscopic group, the primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year rebleeding rate and rebleeding time.

Secondary outcomes

Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse events, quality of life and tolerability of treatment. Following endpoints will be applied, respectively: (1) overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the occurrence of venous thrombosis, (4) the occurrence of adverse events, (5) quality of life

(QOL) score and (6) KPS score. Occurrence of adverse events, QOL score and KPS score are treated as the reflection of safety and tolerability of treatment. Length stay and intra-hospital mortality will be recorded also to this end and treated as outcome candidates. Also, serum markers will be introduced for monitor of change on liver functions and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
QOL			x	x	x	x	x
KPS			x	x	x	x	x

Assessments

Time points of involved assessments to be performed are outlined in Table 1. For participants allocated to either the groups, the following assessments will be performed and corresponding data will be collected:

1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
2. Transjugular measurement of HVPG.
3. Disease history with clear record about the number of occurrence of gastroesophageal variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal syndrome and hepatopulmonary syndrome, etc.
4. Clinical diagnosis and etiology for cirrhosis.
5. Laboratory test results including red blood cells, white blood cells, hemoglobin, blood ammonia, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum

creatinine.

6. Color Doppler ultrasound results including general condition of spleen and liver, spleen diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous reflux, cardiac output, left ventricular ejection fraction and heart output.

7. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.

8. Abdominal CT scans.

9. Esophagogastroduodenoscopy results including the location, classification, diameter of varices and red signs.

10. Electrocardiogram results.

11. Child-Pugh score and classes.

12. Model for end-stage liver disease (MELD) score.

13. QOL score.

14. KPS score.

15. Adjustment records of dosage of propranolol.

16. Adverse events and severe adverse events of any cause.

17. Length stay.

Upon occurrence of the first variceal rebleeding after the operative intervention, the following data will be additionally collected:

1. Cause of rebleeding.

2. Time of rebleeding since enrollment.

3. Treatment and outcome of the rebleeding.

Upon death of a participant, the following data will be additionally collected:

1. Time of death since enrollment.

2. Cause of death.

Sample size estimation

No study has yet compared the outcome between cirrhotic patients with gastroesophageal variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy plus propranolol oral administration, the sample size is determined based on pooled data of

variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy plus propranolol oral administration is estimated by 6 randomized controlled trials (Table 2).[22-27] The variceal rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).[20 28-32] Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44% and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate (1-β) of 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

Ethics and dissemination

Ethical approval was obtained from all three participating centers. Any modifications in protocol will be done under the premise of adequate communication and approval. All interventions and assessments included in this trial will be in full compliance with Good Clinical Practice (GCP).

Before the allocation, all participant candidates will be fully informed about the purpose, process and possible consequences of the trial. Before any treatment, the participants will be informed about the interventions they will undergo and the interventions will not be applied before a written informed consent signed by the participants themselves is provided.

The result of this trial (CHESS1803) will be presented at national and international conferences and published in peer-reviewed journals.

Safety

Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic therapy is generally implemented worldwide. Both surgical interventions showed low risks of severe adverse events. Nevertheless, the participants and whose relatives will be able to contact the study team when any severe adverse event or disease complication occurs. The participants will receive proper treatments as soon as feasible.

The following data will be recorded when an adverse event occurs:

1. The exact kind of adverse event.
2. The starting, ending and reporting time of the adverse event.
3. Severity of the adverse event.
4. Treatment and outcome of the adverse event.

Adverse events will be documented and reported to the investigators and ethics board of the involved center in 48h. Severe adverse events will be documented and reported to the investigators and ethics board of the involved center, principle investigator and supervision departments required by GCP immediately.

Data management

For imaging data, the electronic form images will be collected. Other raw data will be recorded in the written form case report form first and saved electronically afterwards. All electronic data will be kept by a member of the study team without direct clinical contact with any of the centers. All written form data will be stored in cabinets with lock permitting access for only investigators. All data will be kept for 25 years after publication and destroyed after then.

Statistical analyses

Statistical analyses will be performed in intention-to-treat cases. A case will be censored when the participant received liver transplantation. Subgroup analysis will be performed for Child-Pugh class A and class B patients respectively. Continuous variables will be shown as mean (±SE) or median (range). No interim analyses will be conducted on the primary

outcome. Multivariate COX regression model including age, sex, platelet, HVPG, aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, MELD score and Child-Pugh score as confounders will be introduced for analyses of variceal rebleeding and survival, while applying Kaplan-Meier analysis with Log-rank test for inter-group comparison. Occurrence data including variceal rebleeding, overall survival, hepatocellular carcinoma and portal venous thrombosis will be compared using the chi square test. The occurrence of all adverse events will also be collected, described and compared using chi square test overall and specifically. For data with repeated measurements including QOL score, KPS score and laboratory tests results, repeated measures ANOVA will be applied. Student's t test or Wilcoxon rank sum test (for continuous data) and chi square test or Fisher's exact test (for discrete variable) will be applied for analyses of other unmentioned outcomes. All results will be presented with 95% CIs.

DISCUSSION

To the best of our knowledge, this study is the first to compare the effectiveness and safety of laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line therapy recommended by international guidelines,[3 5] under an HVPG-guided manner. The risk stratification performance of HVPG has been receiving more concentration and several attempts have been made on HVPG-guided therapy.[33 34] By introducing HVPG restriction as an eligibility criterion, this study targets the population that faces high risk of variceal rebleeding and death[6 8-11] better, enabling exploration of better management for these patients as well as extension of clinical performance of HVPG.

The first splenectomy and pericardial devascularization was performed by Hassab in 1964[35] and modified by Qiu Fazu in 1981.[36] Benefitted from the rapid development of laparoscopic equipment and techniques, surgical procedures for variceal bleeding are becoming decreasingly invasive and also with much lower occurrence of adverse events.[20 29 37-39] Such laparoscopic therapy has been accepted as one of the most common used methods for variceal bleeding in Asia-pacific countries. Pericardial devascularization and splenectomy increase the blood flow of hepatic artery while lower portal pressure and ameliorate leukopenia and thrombocytopenia. Thus, laparoscopic therapy is considered an effective method for variceal

bleeding while benefitting liver function with satisfying performance on long-term survival and general condition of patients. However, it is also reported to be correlated with high occurrence of portal venous thrombosis[40] and exacerbation of portal hypertensive gastropathy.[41] Therefore, a multicenter prospective study about laparoscopic therapy will provide valuable information for the clarification of its influence to the overall outcome. Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy and widely served as control groups in many studies.[22-27 42] On the contrary, studies about laparoscopic therapy are mainly single-arm[20 32 43] or compared with variants and other surgeries.[28-31 40 44 45] To the best of our knowledge, there haven't been any trials about laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls. Thus, this study will also provide data with better comparability to other commonly used therapies.

Still, this study has several limitations. First, this is the first prospective study investigating the HVPG-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic therapy plus propranolol. The lack of enough previous studies may lead to deviations in sample size estimation. Second, the major cause of cirrhosis of the target population of this study is hepatitis B virus infection while it is more complex in American and European countries. Differences in etiology may bring problems in applicability. Third, the period of follow-up in this study is set to be about one year, which may not be enough to thoroughly unfold the long-term effect of laparoscopic therapy.

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Contributors Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang, Lei Li and Chuan Liu are responsible of the data collecting and management. Ruoyang Shao and Yanna Liu drafted this manuscript. Ruizhao Qi, Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version of the manuscript was reviewed and approved by all authors.

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Disclaimer The funders do not participate in the design, recruitment, intervention, data collection, data management and analysis of the study and the preparation and revision of this protocol.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study has been approved by the ethics committee of Shunde Hospital, Southern Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou University (LDYYLL2019-179).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data from this study will be made available upon reasonable request. To request for data, please contact the corresponding author.

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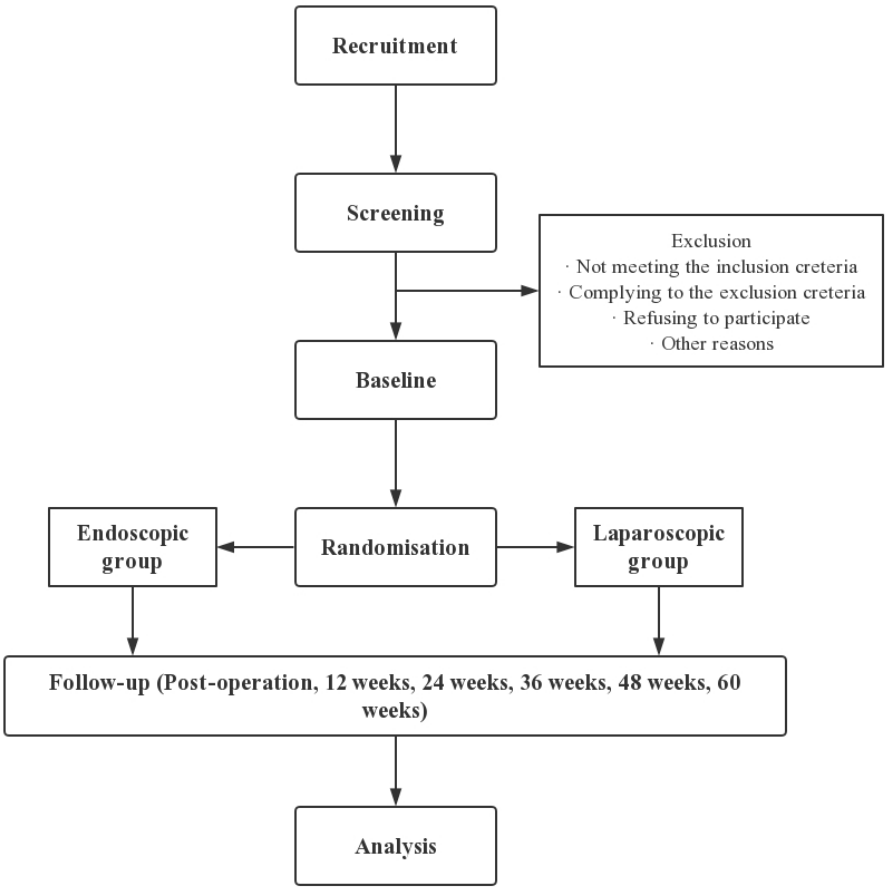
Figure 1 Flow chart for study design.



Flow chart for study design.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 65)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 15/line 386)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 14/line 369)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
(P 15/line 390)	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale (P 4/line 84)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives (P 5/line 123)	7	Specific objectives or hypotheses

Trial design (P 6/line 139)	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting (P 6/line 139)	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria (P 6/line 147)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions (P 7/line 184)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes (P 8/line 213)	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline (P 9/line 228)	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size (P 11/line 267)	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment (P 7/line 167)	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation: (P 7/line 176)		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods (P 9/line 230)	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management (P 12/ line 310)	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods (P 13/line 318)	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
(P13/line 319)	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms (P 12/line 294)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval (P 15/line 397)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments (P 11/line 281)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent (P 11/line 286)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality (P 12/line 309)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests (P 15/line 392)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data (P 12/line 309)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care (P12/line 293)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy (P 11/line 281)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials (supplementary file)	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial in China

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TITLE PAGE

Title:

Hepatic venous pressure gradient-guided laparoscopic splenectomy and pericardial devascularization versus endoscopic therapy for secondary prophylaxis for variceal rebleeding in portal hypertension (CHESS1803): Study protocol of a multicenter randomized controlled trial in China

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ABSTRACT

Introduction

Gastroesophageal variceal bleeding is one of the most common and severe complications with high mortality in cirrhotic patients who developed portal hypertension. Hepatic venous pressure gradient (HVPG) is a globally recommended golden standard for portal pressure assessment and an HVPG ≥ 16mmHg indicates a higher risk of death and rebleeding. This study aims to compare the effectiveness and safety of splenectomy and pericardial devascularization (laparoscopic therapy) plus propranolol and endoscopic therapy plus propranolol for variceal rebleeding in cirrhotic patients with HVPG between 16 and 20 mmHg.

Methods and analysis

This is a multicenter, randomized, controlled, clinical trial. Participants will be 1:1 assigned randomly into either laparoscopic or endoscopic groups. 40 participants whose transjugular HVPG lies between 16 and 20 mmHg with a history of gastroesophageal variceal bleeding will be recruited from three sites in China. Participants will receive either endoscopic therapy plus propranolol or laparoscopic therapy plus propranolol. The primary outcome measure will be occurrence of gastroesophageal variceal rebleeding. Secondary outcome measures will include: overall survival, occurrence of hepatocellular carcinoma, occurrence of venous thrombosis, occurrence of adverse events, quality of life and tolerability of treatment. Outcome measures will be evaluated at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks. Multivariate COX regression model will be introduced for analyses of occurrence data and Kaplan-Meier analysis with Log-rank test for inter-group comparison.

Ethics and dissemination

Ethical approval was obtained from all three participating sites. Primary and secondary outcome data will be submitted for publication in peer-reviewed journals and widely disseminated.

Trial registration number

NCT03783065; Pre-results.

Trial status

Recruitment for this study started on December 2018 while the first participant was randomized on January 2019. Recruitment is estimated to stop on October 2019.

Strengths and limitations of this study

- This study is the first trial that concentrates on the best management on prevention of rebleeding for cirrhotic patients with HVPG between 16 and 20 mmHg.
- This trial is the first one to compare the effectiveness of laparoscopic therapy plus propranolol to endoscopic therapy plus propranolol recommended by international guidelines.
- The surgical procedure involved in this study employs minimally invasive laparoscopy instead of conventional operation, minimizing trauma and complications.
- Limitations of this trial include the lack of accessible data for sample size estimation, potential influence in applicability in other countries due to etiological differences and the relatively short follow-up period.

INTRODUCTION

Cirrhosis is the result of multiple liver diseases and is accounted as a dynamic process.[1] Portal hypertension is a vital event in the natural progression of cirrhosis that is responsible for decompensating events like gastroesophageal variceal bleeding, ascites and hepatic encephalopathy. Gastroesophageal varices could be seen in about 50% of cirrhotic patients and those who developed variceal bleeding face a mortality of 5-20%.[2,3] Thus, the stratification and applicable secondary prevention for patients with high risk is of great clinical significance.

Hepatic venous pressure gradient (HVPG) is the difference between the wedged hepatic venous pressure and free hepatic venous pressure.[4] Eliminating the influence of abdominal pressure, HVPG is currently the most widely accepted reflection of portal pressure, and has been demonstrated to have good performances in risk stratification [3,5] and predicting the

response to treatments.[6,7] An HVPG over 12 mmHg suggests the occurrence of gastroesophageal variceal bleeding.[8] Patients with HVPG over 16mmHg face higher risk of death [8,9,10,11] and rebleeding,[6] while an HVPG over 20 mmHg predicts failure to control bleeding, early rebleeding, and death due to acute variceal hemorrhage.[12,13] Currently, international guidelines recommend endoscopic therapy combined with non-selective beta-blockers to be the first-line therapy of secondary prevention for cirrhotic patients with gastroesophageal variceal bleeding.[3,5] Nevertheless, patients with high HVPG still suffer from risk of treatment failure. Recent years, early transjugular intrahepatic portal-systemic shunts is recommended as a better choice for patients with HVPG $\geq$ 20 mmHg,[14,15] while there still lack a strong evidence to determine the best method for patients with HVPG between 16 and 20 mmHg.

Splenectomy and pericardial devascularization, first performed by Hassab,[16,17] is a promising surgical procedure for cirrhotic patients with gastroesophageal variceal bleeding, especially for those with hypersplenism. With the rapid advance of laparoscopic techniques, since the first laparoscopic splenectomy was reported in 1991,[18] post-operational complications which used to be a major concern of Hassab's operation have been cut down to a great extent due to less invasive procedures.[19] Laparoscopic splenectomy and pericardial devascularization (laparoscopic therapy) has been widely accepted for variceal bleeding in Asia-pacific countries, where the predominant etiology of cirrhosis is hepatitis B virus infection[20] combined with very high occurrence of hypersplenism.[21] However, there haven't been any prospective trials comparing the effectiveness of laparoscopic therapy plus propranolol to the internationally recommended first-line therapy. Also, the precise indication to perform laparoscopic therapy is still unclear.

In this study, the outcomes of recruited patients whose HVPG lies within 16 and 20 mmHg will be compared to explore the optimized management. Taking into consideration the preferred performance of HVPG in risk stratification and the lack of prospective study in long-term performance of laparoscopic therapy, this trial will be meaningful for both the extension of HVPG risk stratification and the clarification of laparoscopic therapy indication.

Objectives

The aim of this trial is to assess the effectiveness and safety of laparoscopic therapy plus propranolol as first-line therapy of variceal rebleeding prevention for cirrhotic patients whose transjugular HVPG lies between 16 and 20 mmHg with gastroesophageal variceal bleeding compared with endoscopic therapy plus propranolol. The primary outcome will be variceal rebleeding. Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse events, quality of life and tolerability of treatment. We hypothesise that:

1. Compared to endoscopic therapy plus propranolol, laparoscopic therapy plus propranolol is more effective in reducing variceal rebleeding.
2. Participants receiving laparoscopic therapy plus propranolol show non-inferior overall survival over those receiving endoscopic therapy plus propranolol.
3. Participants receiving laparoscopic therapy plus propranolol show lower occurrence of hepatocellular carcinoma over those receiving endoscopic therapy plus propranolol.

METHODS AND ANALYSIS

Study design

This study is a multicenter, prospective, randomized controlled clinical trial. The overview of the study process is illustrated in Figure 1. After screened for eligibility and measurement of HVPG, the participants will be randomly allocated to laparoscopic group or endoscopic group. After the operative intervention, there will be a 60-week follow-up period. All tests and interventions will be performed at three involved centers in China: (1) Shunde Hospital, Southern Medical University, (2) Xingtai People's Hospital and (3) The First Hospital of Lanzhou University.

Eligibility criteria

Inclusion criteria

Eligible participants should be (a) aged between 18 to 75 years, (b) clinically and/or pathologically diagnosed cirrhosis with portal hypertension, (c) with a history of gastroesophageal variceal bleeding (melena, hematemesis etc.), without receiving splenectomy or any secondary prevention, (d) screened with transjugular HVPG between 16 and 20 mmHg after hospitalization, (e) with Eastern Cooperative Oncology Group (ECOG)

score ≤ 2 and Karnofsky performance status (KPS) score ≥ 60 during screening, (f) assessed to be Child-Pugh class A or B, and (g) voluntarily participate in the study and able to provide written informed consent and able to understand and willing to comply with the requirements of the study.

Exclusion criteria

Those who conforms to any of the following would be excluded: (a) pregnant or breastfeeding women, (b) with prior known or suspected malignancy (hepatocellular carcinoma, cholangiocarcinoma etc.), (c) with limited coagulation situation (Quick < 50%, partial thromboplastin time (PTT) > 50 sec, platelet count < 50000 / μl or qualitative platelet dysfunction that affects conglutination function of congenital (Bernard-Soulier syndrome, Glanzmann thrombasthenia, storagepool disease, aspirin-like defects, platelet-type Von Willebrand disease, etc) or acquired (medication or other systemic diseases) causes), (d) with massive ascites, (e) assessed to be Child-Pugh class C, (f) refusing or inadequate for transjugular HVPG measurement, (g) with active bleeding upon screening, (h) patients with recurrent bleeding and (i) with other situations whose existence judged inadequate for participation by the investigators.

Recruitment

Recruitment has started in December 2018 and will continue until the intent sample size has been reached. Participants (n = 40) from China are recruited in three sites through (1) posters, which show the condition of the trial, (2) social media (ie, websites, WeChat) and (3) the advice of the doctors.

Patient and public involvement

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

Randomization

Eligible patients will be randomly allocated (1:1) to either the laparoscopic group or the endoscopic group after signing on an informed consent, before which the patients will be

informed about the trial in detail. The groups will be stratified by Child-Pugh class, age (≤ 60 years or ＞ 60 years) and gender. For the randomization, the randPack package of R software (R Project for Statistical Computing, Vienna, Austria) will be introduced. The randomization will be generated by a statistician independent of the study.

HVPG measurement

Transjugular HVPG measurement will be performed for all participants when screening for eligibility by experienced interventional radiologists. The procedure will be performed using a balloon catheter with a pressure transducer at the tip (Edwards Lifesciences, Irvine, California). At first, a zero measurement will be made with the transducer open to air. After transjugular catheterization, free hepatic venous pressure will be measured in the right hepatic vein at about 1-3 cm from the inferior vena cava. Then, the right hepatic vein will be occluded completely by the inflated balloon, after which will the wedged hepatic venous pressure be measured. The measurement will be continued until the pressure reach a plateau. Measurements will be performed in at least triplicate, and the average value will be used. HVPG is the difference between wedged hepatic venous pressure and free hepatic venous pressure.

Operative interventions

All operative interventions will be performed by trained and experienced specialists affiliated to the university centers. Doppler ultrasonography, computed tomography (CT), electrocardiogram and esophagogastroduodenoscopy will be performed routinely pre-operation.

Participants assigned to the laparoscopic group will undergo laparoscopic therapy within 48h after randomization. Laparoscopic therapy will be performed as previously described.[20] General anesthesia will be applied for all participants. Major procedures of the operation include splenectomy and the dissection and ligation of short gastric vessels, posterior gastric vessels and all branches of proximal lesser curvature, cardia and lower 6 to 8 cm part of abdominal esophagus from the stomach coronary vein. During the process of

devascularization, the high esophageal branches and heterotopic high esophageal branches will be carefully screened.

Participants assigned to the endoscopic group will undergo initial endoscopic therapy within 48h after randomization. Candidate procedures for endoscopic therapy include endoscopic variceal ligation (EVL), cyanoacrylate glue injection and sclerotherapy. Decision of which procedure to adopt will be made by experienced specialist according to the condition of the participant, while EVL will be considered the first option as recommended by guidelines.[3,5] Treatments will be performed again every 1-2 week until completely eradication of varices.

Propranolol oral administration

Participants assigned to both groups will begin to receive propranolol after the randomization. Propranolol shall be administrated orally while keeping monitoring the heart rate and blood pressure daily, starting from 20-40 mg b.i.d and adjusting every 2 or 3 days (maximum dose: 320 mg/d for participants without ascites, 160 mg/d for participants with ascites) to achieve a resting heart rate of 55-60 beats/min while the systolic blood pressure maintain > 90 mmHg.[5] The dose can always be adjusted according to the response on participants.

Outcomes and assessments

Primary outcome

In order to compare the effectiveness of laparoscopic group with endoscopic group, the primary outcome of the study is set to be variceal rebleeding. Endpoints will be 1-year rebleeding rate and rebleeding time.

Secondary outcomes

Secondary outcomes include: death, hepatocellular carcinoma, venous thrombosis, adverse events, quality of life and tolerability of treatment. Following endpoints will be applied, respectively: (1) overall survival, (2) the occurrence of hepatocellular carcinoma, (3) the occurrence of venous thrombosis, (4) the occurrence of adverse events, (5) quality of life

(QOL) score and (6) KPS score. Occurrence of adverse events, QOL score and KPS score are treated as the reflection of safety and tolerability of treatment. Length stay and intra-hospital mortality will be recorded also to this end and treated as outcome candidates. Also, serum markers will be introduced for monitor of change on liver functions and compared between two groups.

Table 1 Assessments and time points

Assessment	Time points						
	Pre-operation	Post-operation	12w	24w	36w	48w	60w
HVPG measurement	x						
Laboratory tests	x		x	x	x	x	x
Color Doppler ultrasound	x						
Liver stiffness	x						
CT	x						
Esophagogastroduodenoscopy	x	x					
Electrocardiogram	x						
QOL			x	x	x	x	x
KPS			x	x	x	x	x

Assessments

Time points of involved assessments to be performed are outlined in Table 1. For participants allocated to either the groups, the following assessments will be performed and corresponding data will be collected:

1. Demographic characteristics including gender, height, weight, date of birth and ethnic.
2. Transjugular measurement of HVPG.
3. Disease history with clear record about the number of occurrence of gastroesophageal variceal bleeding and other complexes including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, electrolyte imbalance, portal venous thrombosis, hepatorenal syndrome and hepatopulmonary syndrome, etc.
4. Clinical diagnosis and etiology for cirrhosis.
5. Laboratory test results including red blood cells, white blood cells, hemoglobin, blood ammonia, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct and indirect bilirubin, glutamine transferase, alanine aminotransferase, aspartate aminotransferase, albumin and serum

creatinine.

6. Color Doppler ultrasound results including general condition of spleen and liver, spleen diameter, portal vein diameter, portal vein velocity, splenic vein velocity, splenic venous reflux, cardiac output, left ventricular ejection fraction and heart output.

7. Liver stiffness and spleen stiffness assessed by FibroTouch or FibroScan.

8. Abdominal CT scans.

9. Esophagogastroduodenoscopy results including the location, classification, diameter of varices and red signs.

10. Electrocardiogram results.

11. Child-Pugh score and classes.

12. Model for end-stage liver disease (MELD) score.

13. QOL score.

14. KPS score.

15. Adjustment records of dosage of propranolol.

16. Adverse events and severe adverse events of any cause.

17. Length stay.

Upon occurrence of the first variceal rebleeding after the operative intervention, the following data will be additionally collected:

1. Cause of rebleeding.

2. Time of rebleeding since enrollment.

3. Treatment and outcome of the rebleeding.

Upon death of a participant, the following data will be additionally collected:

1. Time of death since enrollment.

2. Cause of death.

Sample size estimation

No study has yet compared the outcome between cirrhotic patients with gastroesophageal variceal bleeding receiving either laparoscopic therapy or endoscopic therapy. Also, because of the lack of study restricting HVPG baseline level and studies about laparoscopic therapy plus propranolol oral administration, the sample size is determined based on pooled data of

variceal rebleeding rate of several studies including endoscopic therapy plus propranolol oral administration or laparoscopic therapy. The variceal rebleeding rate of endoscopic therapy plus propranolol oral administration is estimated by 6 randomized controlled trials (Table 2).[22,23,24,25,26,27] The variceal rebleeding rate of laparoscopic therapy is estimated by 6 retrospective studies (Table 2).[20,28,29,30,31,32] Pooled rates of variceal rebleeding for endoscopic group and laparoscopic group are 44% and 6%, respectively. Considering a type I error rate (α) of 5% and a type II error rate (1-β) of 20% and a dropout rate of 10%, the calculated sample size for this trial is 40.

Table 2 Variceal rebleeding rates in cirrhotic patients with portal hypertension bleeding treated by endoscopic therapy plus propranolol or laparoscopic therapy: a review of 12 studies.

Laparoscopic therapy			Endoscopic therapy plus propranolol		
First author, year	Number of patients	Number of rebleeding (%)	First author, year	Number of patients	Number of rebleeding (%)
Zheng, 2018	250	9 (3.6%)	Lv, 2018	25	13 (52%)
Bai, 2017	40	2 (5%)	Holster, 2016	35	10 (28.6%)
Bao, 2017	76	19 (25%)	Luo, 2015	36	21 (58.3%)
Cheng, 2014	204	7 (3.4%)	Hung, 2012	47	22 (46.8%)
Jiang, 2009	26	0 (0%)	Sauer, 2002	40	12 (30%)
Wang, 2008	22	0 (0%)	Rössle, 1997	62	29 (46.8%)

Safety

Laparoscopic therapy is accepted and performed in Asia-pacific countries, while endoscopic therapy is generally implemented worldwide. Both surgical interventions showed low risks of severe adverse events. Possible risks related to interventions include: adverse events related to HVPG measurement (including but not limited to arrhythmia, allergy, intraoperative hemorrhage and ecchymoma) endoscopic therapy (including but not limited to nausea, vomit, fervescence, esophagostenosis, esophageal ulcer, dysphagia and early rebleeding), laparoscopic therapy (including but not limited to intraoperative hemorrhage, portal vein thrombosis, subphrenic infection, pancreatic fistula and early rebleeding) and side-effects of propranolol. Participants and whose relatives will be able to contact the study team when any severe adverse event or disease complication occurs. The participants who rebled will receive

proper treatments according to the recommendations of the Baveno VI guideline[3] as soon as feasible. Liver transplantation will be performed in an expedite manner in cases it is needed.

The following data will be recorded when an adverse event occurs:

1. The exact kind of adverse event.
2. The starting, ending and reporting time of the adverse event.
3. Severity of the adverse event.
4. Treatment and outcome of the adverse event.

Adverse events will be documented and reported to the investigators and ethics board of the involved center in 48h. Severe adverse events will be documented and reported to the investigators and ethics board of the involved center, principle investigator and supervision departments required by GCP immediately.

Data management

For imaging data, the electronic form images will be collected. Other raw data will be recorded in the written form case report form first and saved electronically afterwards. All electronic data will be kept by a member of the study team without direct clinical contact with any of the centers. All written form data will be stored in cabinets with lock permitting access for only investigators. All data will be kept for 25 years after publication and destroyed after then.

Statistical analyses

Statistical analyses will be performed in intention-to-treat cases. A case will be censored when the participant received liver transplantation. Subgroup analysis will be performed for Child-Pugh class A and class B patients respectively. Continuous variables will be shown as mean (±SE) or median (range). No interim analyses will be conducted on the primary outcome. Multivariate COX regression model including age, sex, platelet, HVPG, aspartate aminotransferase, alanine aminotransferase, albumin, total bilirubin, MELD score and Child-Pugh score as confounders will be introduced for analyses of variceal rebleeding and survival, while applying Kaplan-Meier analysis with Log-rank test for inter-group comparison. Occurrence data including variceal rebleeding, overall survival, hepatocellular

carcinoma and portal venous thrombosis will be compared using the chi square test. The occurrence of all adverse events will also be collected, described and compared using chi square test overall and specifically. For data with repeated measurements including QOL score, KPS score and laboratory tests results, repeated measures ANOVA will be applied. Student's t test or Wilcoxon rank sum test (for continuous data) and chi square test or Fisher's exact test (for discrete variable) will be applied for analyses of other unmentioned outcomes. All results will be presented with 95% CIs.

DISCUSSION

To the best of our knowledge, this study is the first to compare the effectiveness and safety of laparoscopic therapy plus propranolol with endoscopic therapy plus propranolol, the first-line therapy recommended by international guidelines,[3,5] under an HVPG-guided manner. The risk stratification performance of HVPG has been receiving more concentration and several attempts have been made on HVPG-guided therapy.[33,34] By introducing HVPG restriction as an eligibility criterion, this study targets the population that faces high risk of variceal rebleeding and death[6,8,9,10,11] better, enabling exploration of better management for these patients as well as extension of clinical performance of HVPG.

The first splenectomy and pericardial devascularization was performed by Hassab in 1964 [35] and modified by Qiu Fazu in 1981.[36] Benefitted from the rapid development of laparoscopic equipment and techniques, surgical procedures for variceal bleeding are becoming decreasingly invasive and also with much lower occurrence of adverse events.[20,29,37,38,39] Such laparoscopic therapy has been accepted as one of the most common used methods for variceal bleeding in Asia-pacific countries. Pericardial devascularization and splenectomy increase the blood flow of hepatic artery while lower portal pressure and ameliorate leukopenia and thrombocytopenia. Thus, laparoscopic therapy is considered an effective method for variceal bleeding while benefitting liver function with satisfying performance on long-term survival and general condition of patients. However, it is also reported to be correlated with high occurrence of portal venous thrombosis[40] and exacerbation of portal hypertensive gastropathy.[41] Therefore, a multicenter prospective study about laparoscopic therapy will provide valuable information for the clarification of its influence to the overall outcome.

Endoscopic therapy plus non-selective beta blockers is recommended as the first-line therapy and widely served as control groups in many studies.[22,23,24,25,26,27,42] On the contrary, studies about laparoscopic therapy are mainly single-arm[20,32,43] or compared with variants and other surgeries.[28,29,30,31,40,44,45] To the best of our knowledge, there haven't been any trials about laparoscopic therapy using endoscopic therapy plus non-selective beta blockers as controls. Thus, this study will also provide data with better comparability to other commonly used therapies.

Still, this study has several limitations. First, this is the first prospective study investigating the HVPG-guided therapeutic effect of laparoscopic therapy plus propranolol and endoscopic therapy plus propranolol. The lack of enough previous studies may lead to deviations in sample size estimation. Second, the major cause of cirrhosis of the target population of this study is hepatitis B virus infection while it is more complex in American and European countries. Differences in etiology may bring problems in applicability. Third, the period of follow-up in this study is set to be about one year, which may not be enough to thoroughly unfold the long-term effect of laparoscopic therapy, the occurrence of hepatocellular carcinoma, especially. Patients with HVPG higher than 10 mmHg suffer from a 6-fold-increased incidence of hepatocellular carcinoma.[46] Due to the effect of lower portal pressure of laparoscopic therapy, we expect a decrease in the incidence of hepatocellular carcinoma. We may not be likely to observe this difference owing to the short designed follow-up duration. However, follow-up will still be continued for the participants after the end of this study, somehow making up for this drawback.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the ethics committee of Shunde Hospital, Southern Medical University, the ethics committee of Xingtai People's Hospital, and the ethics committee of The First Hospital of Lanzhou University. Any modifications in protocol will be done under the premise of adequate communication and approval. All interventions and assessments included in this trial will be in full compliance with Good Clinical Practice (GCP).

Before the allocation, all participant candidates will be fully informed about the purpose,

process and possible consequences of the trial. Before any treatment, the participants will be informed about the interventions they will undergo and the interventions will not be applied before a written informed consent signed by the participants themselves is provided.

The result of this trial (CHESS1803) will be presented at national and international conferences and published in peer-reviewed journals.

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Contributors Xiaolong Qi, Weidong Wang, Changzeng Zuo, Zhiwei Li and Xun Li conceived and designed the study. Qingbo Liu, Weijie Zhang, Xiaorong Mao, Xiaojing Song, Jitao Wang, Lei Li and Chuan Liu are responsible of the data collecting and management. Ruoyang Shao and Yanna Liu drafted this manuscript. Ruizhao Qi, Xin Zhao and Xiaolong Qi critically revised the manuscript. The final version of the manuscript was reviewed and approved by all authors.

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Disclaimer The funders do not participate in the design, recruitment, intervention, data collection, data management and analysis of the study and the preparation and revision of this protocol.

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study has been approved by the ethics committee of Shunde Hospital, Southern Medical University (20190104); Xingtai People's Hospital ([2019]001); The First Hospital of Lanzhou University (LDYYLL2019-179).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data from this study will be made available upon reasonable request. To request for data, please contact the corresponding author.

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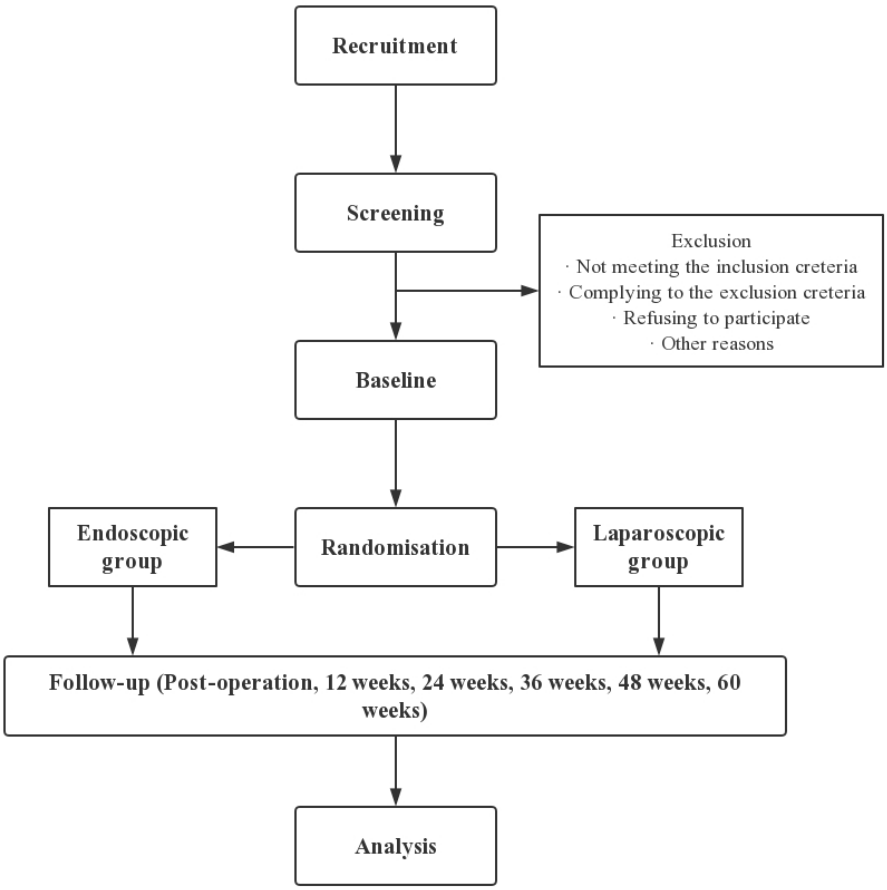
Figure 1 Flow chart for study design.



Flow chart for study design.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title (P 1/line 3)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration (P 3/line 72)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding (P 16/line 433)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P 16/line 419)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
(P 16/line 437)	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale (P 4/line 91)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives (P 5/line 132)	7	Specific objectives or hypotheses

Trial design (P 6/line 147)	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting (P 6/line 147)	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria (P 6/line 156)	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions (P 8/line 211)	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes (P 9/line 242)	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline (P 10/line 257)	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size (P 11/line 299)	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment (P 7/line 181)	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation: (P 7/line 190)		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods (P 10/line 259)	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management (P 13/ line 349)	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods (P 14/line 357)	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
(P14/line 361)	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms (P 13/line 326)	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval (P 17/line 444)	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments (P 12/line 315)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent (P 12/line 319)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality (P 13/line 349)	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests (P 16/line 440)	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data (P 13/line 351)	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care (P13/line 326)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy (P 12/line 323)	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials (supplementary file)	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.