Total Laparoscopic Partial Hepatectomy Versus Open Partial Hepatectomy For Primary Left-Sided Hepatolithiasis: Study Protocol For A Randomized Controlled Trial

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Study protocol

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Abstract

Background: The advantages of laparoscopic left-sided hepatectomy (LLH) for treating hepatolithiasis in terms of the time to postoperative length of hospital stay (LOS), morbidity, long-term abdominal wall hernias, hospital costs, residual stone rate and recurrence of calculus have not been confirmed by a randomized controlled trial. The aim of this trial is to compare the safety and effectiveness of LLH to those of open left-sided hepatectomy (OLH) for the treatment of hepatolithiasis.

Methods: Patients with hepatolithiasis eligible for left-sided hepatectomy will be recruited. The experimental design will produce two randomized arms (laparoscopic and open hepatectomy) at a 1:1 ratio and a prospective registry. All patients will undergo surgery in the setting of an enhanced recovery after surgery (ERAS) program. The prospective registry will be based on patients who cannot be randomized because of the explicit treatment preference of the patient or surgeon or because of ineligibility (not meeting the inclusion and exclusion criteria) for randomization in this trial. The primary outcome is the LOS. The secondary outcomes are percentage readmission, morbidity, mortality, hospital costs, long-term incidence of incisional hernias, residual stone rate and recurrence of calculus. It will be assumed that, in patients undergoing LLH, the length of hospital stay will be reduced by 1.3 days. A sample size of 44 patients in each randomization arm has been calculated as sufficient to detect a 1.3-day reduction in LOS (90% power and $\alpha = 0.05$ (two-tailed)). The trial is a randomized controlled trial that will provide evidence for the merits of laparoscopic surgery in patients undergoing liver resection within an ERAS program.

Discussion: Although the outcomes of LLH have been proven to be comparable to those of OLH in retrospective studies, the use of LLH remains restricted, partly due to the lack of short-and long-term informative RCTs pertaining to patients with hepatolithiasis in ERAS programs. To evaluate the surgical and long-term outcomes of LLH, we will perform a prospective RCT to compare LLH with OLH for hepatolithiasis within an ERAS program.

Trial registration: ClinicalTrials.gov NCT03958825. Registered on 21 May 2019.

Background

Hepatolithiasis is defined as a gallstone disease in the intrahepatic bile ducts and is mainly prevalent in Southeast Asia[1]. Hepatolithiasis may occur alone or with extrahepatic bile duct stones. Long-term hepatolithiasis can cause secondary biliary stricture, liver cirrhosis and even cholangiocarcinoma[2]. Hepatectomy is one of the most effective methods for treating intrahepatic stones because it can simultaneously remove stones and relieve bile duct stricture[3, 4]. For hepatectomy of hepatolithiasis, due to the presence of stones in the left liver of most patients with intrahepatic bile duct stones, left hepatectomy, including left lateral hepatectomy and left hepatectomy, is the most common procedure performed. With the advancement of laparoscopic technology, laparoscopic liver resection has been used in the treatment of various liver diseases, including benign and malignant liver tumors[5, 6]. Since Louisville's statement in 2008, the international status of laparoscopic hepatectomy has been widely recognized[7]. However, laparoscopic hepatectomy in patients with hepatolithiasis may be more difficult and challenging than open hepatectomy because patients with hepatolithiasis usually experience changes in their normal anatomy and perihepatic adhesion due to chronic inflammation[8–10]. To date, only a few retrospective studies have compared the outcomes of laparoscopic left-sided hepatectomy (LLH) with those of open left-sided hepatectomy (OLH) for hepatolithiasis, and the feasibility and efficacy of LLH have not been fully evaluated[11, 12].

Enhanced recovery after surgery (ERAS) programs have been applied for patients receiving small-scale and large-scale liver resection[13, 14]. A number of studies have shown that ERAS programs are safe, feasible and effective in reducing the median LOS in both open and laparoscopic resection[15, 16]. In some retrospective trials comparing earlier recovery or a reduction in LOS, perioperative evaluation or management was not uniform[12, 17]. In addition, the value of laparoscopic left-sided hepatectomy for hepatolithiasis compared with that of open left-sided hepatectomy within an ERAS program in terms LOS and hospital costs has not been studied in a randomized controlled trial (RCT). However, randomized grouping of patients undergoing open or laparoscopic liver resection is dangerous. Due to the lack of clinical and patient equipoise of

laparoscopic surgery, experienced centers and surgeons are reluctant to randomize patients. To take advantage of two centers' preference and disapproval of laparoscopic liver surgery to obtain a series of uninterrupted prospective patients, we constructed a randomized controlled trial design with two randomized groups (open and laparoscopic surgery) and a prospective registry. Combining an RCT with a prospective registry will improve the overall power and enhance the external validity and generalizability of the study results[18].

Methods And Design

A randomized clinical trial and a prospective registry with two parallel groups will be conducted at general surgery department of the Second Affiliated Hospital of Anhui Medical University in China. The aim of this study is to compare the effect of two hepatectomy methods for hepatolithiasis by assessing factors related to mortality and morbidity, including postoperative length of hospital stay, biliary leakage[19], post-hepatectomy hemorrhage[20], post-hepatectomy liver failure[21], incisional hernias, residual stone rate, and recurrence of calculus[22].

Sample size

The sample size calculation is based on the primary endpoint: the LOS. According to published data, an assumed a 1.3-day reduction in LOS is the appropriate basis for the calculation, assuming 4.5 days in the LLH group and 5.8 days in the OLH group[23]. This calculation yields a total of 40 patients in each group, which assures 90% power at a two-sided level of significance of 5% (NCSS and PASS 11 (NCSS Statistical Software, Kaysville, UT, USA)). Assuming an expected withdrawal rate of 10% during the trial, 8 additional patients will be included and randomized; therefore, the total sample size required is $n = 88$ patients. Figure 1.

Eligibility criteria

Inclusion criteria

Patients who meet the following criteria will be included in the study:

1. Patients suitable for undergoing both laparoscopic left hepatectomy and open left hepatectomy of the liver
2. Patients who be able to understand the nature of the study and what will be required of them
3. Men and nonpregnant, nonlactating women between the ages of 18 and 80
4. Patients with ASA I-III.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Inability to provide informed consent
2. Patients associated with a tumor or who require bilioenteric anastomosis or left caudate lobectomy
3. Immunodeficiency disease, such as HIV
4. Previous upper abdominal surgery (except for laparoscopic and open cholecystectomy).

Withdrawal

Patients can withdraw from the trial at any time at their own request or at the request of their legal representative. Patients may be removed if, in the researchers' opinion, continuing the trial may be detrimental to the patient's health, if left hepatectomy is not performed due to a technical inability, or for other reasons. Every withdrawal will be recorded in the clinical report forms (CRFs) and in the patient's medical case records. All examinations scheduled for the final trial day will be performed on all patients and documented. All dates will be analyzed according to the intention-to-treat (ITT) principle[24].

Ethics, study registration, and consent

The study has been approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (identifier: KY20190809). The trial protocol has also been registered in the protocol registration system at ClinicalTrials.gov (identifier: NCT03958825). Patients willing to participate in this trial will receive both verbal and written information at the time of recruitment in the outpatient clinic of the Second Affiliated Hospital of Anhui Medical University. All participants of the study will be provided a participant information sheet and informed consent form entailing sufficient information. The participants will sign the general consent for the further use of personal data and biologic material. The investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws and/or the corresponding section of the study specific consent. The study procedure, benefits, risks, and data management will be clarified in detail during the preoperative conversation. All trial data will be saved and stored on a server during the trial, and patients will be asked to agree to future analysis.

Trial interventions

The procedures of LLH

The LLH operative procedures will be completed by the same surgical team in each group led by two experienced board-certified surgeons. LLH and left lateral segmentectomy will be performed with the patient in the French position, with two experienced surgeons at each side (bilateral two chief surgeons) and a video laparoscope operator between the legs, which is different from the classic laparoscopic technique. Laparoscopic operations will be performed using 5 trocars. Common bile duct exploration (CBDE) will be performed in all patients with suspected stones in a dilated common bile duct (> 10 mm) using a choledochoscope, followed by T-tube placement if postoperative cholangiography is required[12]. Figure 3.

The procedures of OLH

OLH will be performed under general anesthesia with the patient in the supine position. An inverted L-shaped incision will be performed. The left hepatic artery and left portal vein will be individually dissected, ligated, and divided. Then, the left bile duct and left hepatic vein will be ligated, divided, and closed after hepatic parenchymal resection. The CBDE will be the same as the LLH.

Primary and secondary endpoints

Primary endpoint

The LOS is designated as the primary outcome of this trial. Only the researchers and surgical surgeons will know the true operation. A blinded ward doctor will decide whether the patient should be discharged.

Secondary endpoints

The secondary outcomes are biliary leak[19], hemorrhage[20], post-hepatectomy liver failure[21], wound infection, intra-abdominal fluid collection or abscess, relaparotomy, mortality, long-term abdominal wall hernias, hospital costs, residual stone rate and recurrence of calculus[22]. Existent ISGLS definitions will be used to ensure the comparability and generalizability of the results. Postoperative complications will be graded based on severity according to the Clavien-Dindo definition[25]. Table 1 and Table 2.

Table 1
Definition of the endpoints

Endpoints	Definition and assessment of outcomes
postoperative length of hospital stay	Time from the day of the operation until discharge (days)
Operative time	Time from the beginning to end of the operation
Mortality	Death due to any cause until 90 days after the operation and the reason
Morbidity	Postoperative complications will be recorded until 90 days after the operation. The severity of complications will be graded according to the Clavien-Dindo classification ^[25]
Blood loss	Total blood loss during the operation
Intraoperative blood transfusion	Massive hemorrhage with a hemoglobin level < 7 g/dl or Hct < 22
postoperative length of hospital stay	Time from the day of the operation until discharge (days)
Post-hepatectomy hemorrhage	Evidence of blood loss from drains and/or nasogastric tube based on ultrasonography, as defined by ISGPS (grade A, B or C) ^[20]
Biliary leak	Bilirubin concentration in the drain fluid at least three times the serum bilirubin concentration, as defined by ISGLS (grade A, B or C) ^[19]
Post-hepatectomy liver failure	The impaired ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5, as defined by ISGLS (grade A, B or C) ^[21]
Intraabdominal fluid collection	Collection of fluid measuring ≥ 3 cm associated with clinical or laboratory abnormalities
Pneumonia	Presence of a new infiltrate on the chest X-ray as well as the following: body temperature $\geq 38^{\circ}\text{C}$, abnormal elevation of WBC, or positive sputum, and requiring antibiotic treatment
Wound infection	Surgical site infection associated with laparotomy that develops during the initial hospital stay
Abdominal rupture	Dehiscence of abnormal closure with the need for resuture of the laparotomy during the initial hospital stay
Total hospitalization expenses	Hospital costs from admission to discharge (\$)
Recurrence of calculus	Calculi in the intrahepatic duct within 3 months after hepatectomy are defined as residual stones ^[22]

Table 2
Severity grade according to the Clavien-Dindo definition[25]

Grade	Definition
0	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological intervention.
I	Requiring pharmacological treatment with drugs other than those allowed for grade 0 complications
II	Requiring surgical, endoscopic or radiological intervention
IIa	Intervention not under general anesthesia
IIb	Intervention under general anesthesia
III	Lifer-threatening complication. Requiring intensive care unit management
IIIa	Single-organ dysfunction
IIIb	Multiorgan dysfunction
IV	Death of patient

Table 3
Schedule of enrollment, interventions, and assessments

Screening		before surgery	surgery	POD1	POD2	POD3	Discharge	POD30	6 months Postop	12 months Postop	24 months Postop
Selection criteria and informed consent	X										
Medical history Demographics	X										
Physical examination	X										
Laboratory tests	X			X	X	X	X	X	X	X	X
Trial intervention			X								
Intraoperative outcomes			X								
Postoperative outcomes				X	X	X	X	X	X	X	X
POD postoperative day, postop postoperatively,											

Type of trial

The trial is a prospective randomized interventional single-center study comparing two parallel groups with a prospective registry to determine whether patients underwent LLS by laparoscopic surgery rather than open surgery with an enhanced recovery program. The types of interventions by patients, nurses, and ward doctors (not the surgeons performing the operations) before postoperative day (POD) 3 will be blinded. However, patients who are randomized to receive open or

laparoscopic liver resection are at risk, as explained earlier. In addition, there is another potential source of bias when randomly selecting patients with strong treatment preferences. When patients are not informed about their treatment allocation (POD 3), they may be resentful and feel demoralized if they do not receive their preferred treatment. Thus, their compliance may be poor. By contrast, patients receiving their preferred treatment may have above-average compliance. Thus, to capitalize on centers both with and without preference for laparoscopic liver surgery and to acquire an uninterrupted prospective series of patients, all nonrandomized patients undergoing LLS will be approached to participate in the prospective registry. Registration of these patients is imperative to guarantee a consecutive series of patients and also because the absence of such a series may restrict the generalization of the results, as randomized participants may not, in fact, be representative[26]. The combination of an RCT and a prospective registry will improve the overall power and strengthen the external validity and generalizability of the study results[15, 27, 28].

Randomization

The randomization sequence is performed with sealed opaque envelopes. Upon completion of the screening assessment, participants who satisfy all the inclusion criteria and none of the exclusion criteria will be randomly assigned to the intervention and control groups in a 1:1 allocation ratio. Randomisation assignment will be computer generated using the 'randomize' library of SPSS22.0 (SPSS, Chicago, USA), with a complete randomising method based on permutations that guarantees balanced groups. A research nurse who will not participate in patient care will perform the randomization. Study group allocation will depend on the contents of sealed opaque envelopes generated in the above-described manner, and envelopes will be opened before operation.

Blinding

The patients and outcome observers will be blinded before POD 3 with respect to the trial intervention. Blinding of the surgeons and people involved in the operation is not feasible due to the nature of the interventions.

Participating surgeons

The surgical experience of surgeons can affect complication rates, which might bias the results. To prevent surgeon bias, surgeons should meet the following criteria: (1) have performed more than 200 open hepatectomies, (2) have performed more than 100 laparoscopic hepatectomies, and (3) be a qualified surgeon according to the China College of Laparoscopic Hepatectomy. LLH will be performed by two surgeons (Hui Hou and CL Wu), and OLH will be performed by three surgeons (Hui Hou, XP Geng and QR Xiong).

Data management and quality assurance

Data is collected prospectively for all patients including history, physical examination, laboratory data, pathologic examination, perioperative clinical information, and complications. Data is collected via datasheets on paper and kept securely. Study subjects will complete the examinations at inclusion, 1 weeks after surgery, and 3, 6, 12, and 24 months postoperatively. Follow-up will be followed up to 24 months postoperatively (Table 1). All handling cases are managed by subject identification code or anonymized registration number. The correspondence table of the anonymizing code and names and the consent form containing the names are kept strictly in the separate lockable document storage. All required parameters are collected in an SPSS data file (SPSS version 25, IBM statistics, Chicago, IL, USA).

ERAS-Program

All patients will participate in the ERAS liver program with a standardized peri-operative management. For the daily guidelines on the pre- and postoperative care of patients undergoing liver resection, see Fig. 2.

Follow-up

Follow-up is conducted at 1 month postoperatively and then 3, 6, 12, and 24 months postoperatively by telephone or as outpatients with liver function test and abdominal ultrasonography for 2 years or until death. CT or MRCP is performed in

cases of suspected stone recurrence or cholangitis.

Statistical analysis

The two-sided null hypothesis for the primary endpoint states that both study interventions will lead to a similar time to the LOS; the alternative hypothesis is that one intervention will perform better than the other. The null hypothesis will be tested by analyzing the covariance while adjusting for age and the type of liver resection. A binary logistic regression will be applied to compare the time to functional recovery between groups after adjusting for other factors. Background characteristics and surgical outcome measures will be compared using chi-squared or Fisher's exact tests for categorical data and two-tailed t-tests or nonparametric Mann-Whitney U tests for continuous variables. Categorical data will be presented as frequencies and group percentages, and continuous variables will be expressed as means and standard deviations. The homogeneity of the two groups will be described by comparison of the demographic data and baseline values. All analyses will be performed on an ITT basis [17]. For the ITT analyses, the data will be processed for all trial patients in their randomized groups. A P-value < 0.05 will be considered statistically significant. All statistical calculations will be performed using SPSS22.0 (SPSS version 25, IBM statistics, Chicago, IL, USA).

Discussion

The left side of the liver is a common site for and more seriously affected by hepatolithiasis. Hepatectomy has been the most effective treatment for removing IHD stones and resolving bile duct strictures, thereby decreasing the risk of recurrence[3, 22]. Compared with open hepatectomy, laparoscopic hepatectomy enables more accurate visualization and vascular anatomy. However, only a few retrospective studies comparing OLH and LLH without the ERAS program have been published summarizing their complications and long-term follow-up dates, such as residual stones and risk of recurrence, which are the main concerns of surgeons[11, 12].

The present study is the first RCT study to compare the benefits of the laparoscopic approach to left-side hepatolithiasis in Chinese patients undergoing hepatectomy with the ERAS program. It is well-recognized that a well-conducted double-blind RCT provides the highest level of evidence to prove the possible benefits of laparoscopic liver resection. However, performing an RCT during surgery is not without difficulties, and alternative trial designs may be necessary[23, 28]. First, the intervention needs to be tested in a standardized environment, and the properties of the intervention should remain unchanged during the trial period. The surgeons should have advanced laparoscopic experience and open liver resection experience. Both LLS and the ERAS program-enhanced recovery protocol provide the standardization needed. Second, the intervention should be double-blinded. Although double blinding in a surgical trial is difficult, using a fixed abdominal dressing for 3 days after surgery is feasible and should prevent both ward caregivers and patients from knowing the type of intervention. The trial with randomization of patients and surgeons with treatment equipoise and a prospective registry to cover both surgeons who believe that, based on their laparoscopic experience, randomization is not ethically justified and patients with a strong treatment preference will provide external validity. This trial design, which capitalizes on rather than ignores the differences between patients, will provide more robust outcome data and should lead to continuous performance monitoring after the trial.

Worldwide, the median LOS at a hospital for open and laparoscopic resections varies from 4 to 8 days[6, 9, 12]. The reasons for delay of discharge and the discharge location are often absent, and to date, a clear definition of recovery has only been used in a few publications. Departing from the standpoint that an RCT should be conducted, a primary question concerns which sample size should be used. In our opinion, a reduction of only 1.3 days in the time to recovery or LOS at a hospital after laparoscopic resection would be a disappointingly low gain. To prove such a reduction, 88 patients are needed ($\alpha = 0.05$ and power of 90%), making the trial unlikely to be reasonably moderate, and it is to be expected that patient accrual will be accomplished within 2–3 years.

This study has several limitations that should be acknowledged. It will be conducted at a single institution. Due to the small sample size, the findings from this trial will not allow for established clinical application but rather will serve to inform the

need for larger multicenter RCTs on LLH for OLH.

Abbreviations

ASA, American Society of Anesthesiologists; CRFs, Clinical Report Forms; ISGLS, International Study Group of Liver Surgery;

Declarations

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Publication policies

The sponsor will make every endeavor to publish the data in a medical journal(s) to communicate the results to healthcare professionals, the public, and other relevant groups. All participants will be sent a free copy of the published article(s). There will not be any publication restriction, and we plan to submit at least three major publications. We will also present preliminary results at national, regional, and international scientific meetings. The main investigators—Dr. Shubo Pan, Dr.Chunli Wu, and Prof. Hui Hou—will be either first or last authors in at least two of the three major publications. All investigators indicated in this protocol, and eventually additional colleagues participating in the future, will be coauthors of this study according to their individual contributions.

Trial status

This protocol represents the trial protocol version 1.0. The study is currently in the process of recruiting participants. Recruitment of participants commenced on 10th August 2019, and will be completed in December 2022.

Author's contributions

SBP conceived the study, drafted the manuscript, and revised the manuscript. XPG conceived the study and critically revised the manuscript. DCZ and HH calculated the sample size. SBP and ZDC drafted the manuscript. CLW and SBP drafted the study protocol. SBP and CLW revised the manuscript. All the authors read and approved the final manuscript.

Authors' information

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was submitted for approval to the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (identifier: KY20190809). We distributed a written consent form to the participating patients and also informed them about the trial orally.

Consent for publication

Not applicable.

Competing interests

The authors declare that no competing interests exist.

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Figures

Figure 1

Flow chart according to CONSORT

ERAS program

Figure 2

ERAS program

Image not available with this version

Figure 3

Surgical techniques for LLH

Supplementary Files

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